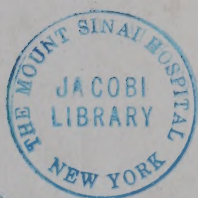





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COMPLICATIONS OF CEREBRAL ANGIOGRAPHY: A SUPPLEMENTARY REPORT

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AND

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Analysis of over 500 consecutive cerebral arteriograms performed at this hospital between 1952 and 1956 revealed an overall incidence of complications of 19 per cent (1). In 12 per cent of these arteriograms the complications were serious though transient. There were permanent sequelae in 3 per cent and there were eight deaths possibly related to the procedure. Diodrast[®] (35%) was the contrast medium used for these angiograms. Since 1956, however, 50 per cent Hypaque[®] has been utilized as the contrast medium for cerebral angiography at this hospital. The purpose of this brief communication is to show that the incidence of complications from arteriography has fallen with the new medium. To demonstrate this the complications of 500 consecutive cerebral arteriograms performed with Hypaque[®] have been analysed.

MATERIALS AND METHODS

The 500 consecutive arteriograms were performed by 12 members of the resident staff. 433 of the angiograms were of a carotid artery; the other 57 were vertebral studies. All procedures were performed percutaneously, and almost all were under local anesthesia. The number and type of complications were determined by retrospective interview with each of the residents who performed the arteriograms. Charts were reviewed when necessary.

A complication is defined as any detrimental alteration in the patient's well being which might possibly be related to the arteriogram.

RESULTS

In this series of 500 consecutive arteriograms, there were 30 complications. The nature of these complications is shown in Table I.

There were three deaths possibly related to arteriography. Two of these patients were terminal prior to the arteriogram. The blood pressure of one could not be maintained despite intravenous vasopressors. The third death occurred in an elderly woman who developed a massive intracranial hemorrhage following an inadvertent sheath injection of 12cc of contrast substance.

There were seven permanent complications in this series. Two of these occurred in patients who had received intracarotid chemotherapy for cerebral malignancies at the time of arteriography. Sixteen of the remaining 20 complications had completely subsided within 72 hours following arteriography. These

From the Department of Neurology, The Mount Sinai Hospital, New York, N. Y.

TABLE I
Complications in 500 consecutive arteriograms with Hypaque®

Complication	Duration	Number
Deaths (2 patients terminal prior to arteriography)		3
Increased generalized neurological deficit	Permanent	5
	24 to 48 hours	2
Increased focal neurological deficit (hemiparesis, field defects, etc.)	Permanent	1
	1 to 3 weeks	4
	12 to 72 hours	5
	Under 6 hours	4
Convulsions	Transient	2
Brachial neuralgia	Permanent	1
	Less than 6 hours	1
Significant neck hematoma	Transient	1
Probable hypersensitivity reaction	Transient	1

transient complications included increased neurological deficit in three patients who received enough sedation prior to the procedure to produce similar transient deficit. Two other patients developed transient complications following arterial puncture, prior to the injection of contrast substance.

The incidence of complications appeared to be appreciably higher following vertebral as compared to carotid arteriography. There were seven complications in the 57 vertebral angiograms performed in this series (12.3%), and 23 complications in the 443 carotid studies (5.2%).

DISCUSSION

The incidence of complications from Hypaque® cerebral arteriography has been found to be 6.0 per cent. In 5.2 per cent of the 500 arteriograms these complications were serious and there were permanent sequellae in 2.0 per cent. Table II compares the incidence of complications reported by several writers utilizing Diodrast® or Hypaque® arteriography.

Our experience, it will be noted, agrees with the general experience of other writers concerning the relative safety of Hypaque® and Diodrast®. Only one report has been found which does not confirm the increased clinical safety of Hypaque® over Diodrast® (19).

Several experimental studies suggest a basis for this relative lack of toxicity of Hypaque®. In several animal species, less damage to the blood brain barrier has been demonstrated to occur with Hypaque® than with other contrast media (12, 15, 20). Hypaque® injected into the aortas of dogs produced less neurological impairment and less histological damage to the spinal cord than a similar injection of Diodrast® (21). Intracarotid Hypaque® produces less change in the cerebral circulation of animals (22), and in the electrocardiogram of man (23) than other contrast media.

The incidence of complications appears higher both in the present series and in the previously reported one from this hospital as compared with those in the

TABLE II
Complications reported with Diodrast® and Hypaque® arteriography

Author	Contrast Medium	Number of Arteriograms	Deaths	Permanent Complications	Transient Complications
Coddon & Krieger (1)	Diodrast 35%	546	8	6	95
Curtis (2)*	Diodrast 35%	720	1	1	5
Dunsmore et al. (3)	Diodrast 35%	147	3	4	7
Abbott, et al. (4)	Diodrast 35%	174	5	4	8
Perese, et al. (5)	Diodrast 35%	234	7	3	19
Kaplan & Walker (6)	Diodrast 35%	500	4	19 other complications	
Segelov (7)	Diodrast 35%	300	0	0	7
Dimant, et al. (8)*	Diodrast	1556	2	13	5
Sedzimir (9)*	Diodrast 42.5%	273	0	0	?
Smolik & Nash (10)	Hypaque 50%	39	0	0	0
Dunn, et al. (11)	Hypaque 50%	50	0	0	2
Whiteleather & DeSaussure (12)	Hypaque 50%	300	0	0	2
Broadbridge (13)	Hypaque 25%	200	0	0	7
Munslow, et al. (14)	Hypaque 50% & Renografin®	150	0	0	4
Lindner, et al. (15)	Hypaque 50%	580	2	0	2
Davis, et al. (16)*	Hypaque 50%	100	?	0	4
Brown & Andy (17)	Hypaque 50%	222	0	0	9
Kuhn (18)	Hypaque 50%	100	0	0	0
Present study	Hypaque 50%	500	3	7	20

* Information concerning complications incomplete.

literature (1). This is probably due to the more stringent criteria employed for the definition of a complication, and possibly for the more detailed and prolonged observation of the patient during and after arteriography in our series.

The value of cerebral arteriography for neurological diagnosis has long been established. The current acceptance of the relative safety of the procedure can perhaps best be demonstrated by the increased utilization of the technique since introduction of the new contrast medium. The previously reported 546 consecutive arteriograms with Diodrast® were performed during a four and one half year period (June 1952–December 1956) (1); the 500 consecutive arteriograms with Hypaque® reported here were performed in a ten month period (June 1958–April 1959).

SUMMARY

A. The overall incidence of complications in 500 consecutive cerebral angiograms with Hypaque® was found to be 6 per cent. Two per cent of these complications were permanent. There were three deaths possibly related to the procedure.

B. Complications followed vertebral arteriography more than twice as frequently as carotid angiography.

C. The safety of cerebral arteriography has been enhanced by the use of Hypaque®.

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ABNORMAL LACTATION

REPORT OF A CASE INDUCED BY RESERPINE AND A BRIEF REVIEW OF THE SUBJECT

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AND

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Lactation as a complication of reserpine therapy has been reported in the foreign literature (1, 2), but it does not appear to be well recognized in this country. Further, a search of the recent American literature has failed to reveal a general review of the subject of abnormal lactation. For these reasons the following case is presented together with a brief discussion of the various causes of galactorrhea.

CASE REPORT

R. McK. (M.S.H. 4061), a 17 year old nulliparous negress has been followed for several years at The Mount Sinai Hospital as an outpatient with numerous admissions to the medical wards for control of hypertension and asthma.

In 1952, at the age of 11 years, she was hospitalized because of nephrotic syndrome with microscopic hematuria. The clinical diagnosis was subacute glomerulonephritis. She improved with ACTH therapy and was discharged. Two subsequent admissions in 1953 and 1954 were for exacerbations of nephrotic syndrome for which she received treatment with various steroids.

Hypertension was first noted in December, 1955 and the patient was treated for five months with 4 mgm of Rauwiloid® daily. Thereafter, she received no antihypertensive medication until September, 1957 when her blood pressure was found to be 210/155. She was given 40 mgm of hydralazine and 0.5 mgm of reserpine daily and her blood pressure fell to 150/105. Subsequently she also received chlorothiazide and mecamlamine. During the next several months she was lost to follow-up, however, she continued to take her medication.

She was next seen in the emergency ward on September 22, 1958 because of an episode of epistaxis. She stated that her only complaint in the interim was tender enlargement of both breasts and intermittent milky discharge from the nipples. Epistaxis was controlled by local measures, but because of hypertension, the patient was admitted to the hospital.

Physical examination revealed a well developed 17 year old negress with epistaxis. The skin was warm, dry and clear. The optic fundi showed grade 2 hypertensive changes. The heart was not enlarged, there were no murmurs, the lungs and abdomen were negative. A small amount of milky fluid could be expressed from both nipples. The blood pressure was 240/170, and the pulse was 100 per minute.

Laboratory studies revealed the hemoglobin to be 10.1 gram per cent, the white cell count to be 4,200 per cu. mm. with a normal differential. Blood urea nitrogen was 15 mgm per cent. The blood sugar was normal. Urinalysis revealed a specific gravity of 1.010, 1 plus protein, 3 to 5 red and 2 to 4 white blood cells in the sediment per high-power dry, microscopic field. Skull x-rays revealed a normal sella turcica.

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Since the cause of her abnormal lactation was not immediately recognized, the dosage of reserpine was increased to 0.75 mgm daily; in addition she received chlorothiazide, mecamlamine and hydralazine. Within 13 days secretions from both breasts became copious. She was maintained on the same medication during the next two weeks after which reserpine alone was discontinued. Within six days the patient's breasts became smaller, less tender and no secretions could be expressed. Urinary FSH levels during lactation were positive at 5, 10 and 50 mouse units, values which are considered elevated for the patient's age group.

Her blood pressure controlled, the patient was discharged in October, 1958. She was to continue taking the above medicines with the exception of reserpine. During the next four months the patient experienced no galactorrhea or any other complaints referable to her breasts.

In February, 1959, she consented to another trial of reserpine therapy. She received 1 mgm of the drug daily and within one week she began to lactate. Galactorrhea persisted during the second week of reserpine administration. Lactation ceased three days after and she has had no recurrence since the drug was withheld.

In view of the elevated urinary FSH values demonstrated while she was receiving reserpine and lactating, urinary FSH levels were determined when the patient had neither received the drug nor lactated for two months. Results were positive at 10 but negative at 50 and 100 mouse units (normal).

It should be mentioned that during her illness the patient had no menstrual irregularities and she denied any mechanical stimulation of her breasts.

DISCUSSION

The understanding of abnormal lactation requires some familiarity with the physiological mechanism of normal lactation. While the detailed aspects of this subject are not yet completely understood, it is generally accepted that initiation and maintenance of lactation are influenced by mechanical, humoral and psychic factors.

Suckling maintains persistent lactation until the time of weaning. In addition, the perception of the mechanical stimulus results in a sensory impulse traveling through nervous pathways via the hypothalamus to the posterior pituitary, which causes the release of oxytocin, which in turn stimulates the ejection of milk, the so-called let down effect (3, 4). Other humoral factors of importance are: prolactin (luteotrophic hormone), produced by the pituitary; the ovarian hormones, estrogens and progesterone, which in large doses can also inhibit lactation; thyroxin; adrenal factors and insulin (5).

The role of the psyche in normal lactation was studied by Newton and Newton who demonstrated that mothers with a positive attitude gave larger amounts of milk than those who were negativistic toward breast feeding (6).

Abnormal production of milk may be induced by a variety of stimuli, extrinsic or intrinsic, acting as trigger factors at various levels of the normal regulatory pathways of lactation.

Among extrinsic agents capable of producing galactorrhea are exogenous drugs. In the patient presented above lactation could be initiated and terminated at will with the administration and withdrawal of a therapeutic dose of reserpine. This side effect of the drug must be relatively rare, few cases have

been previously reported, and it is not included in a recent major review on the complications of reserpine therapy (7).

The lactogenic effect of reserpine has been demonstrated in estrogen-primed rabbits that were injected with the drug (8, 9). The mechanism of this response was recently elucidated by Meites who demonstrated an increase of pituitary prolactin in rabbits following injection of reserpine (10).

Chlorpromazine has also been reported to induce lactation (11, 12). Robinson reported a ten per cent incidence of galactorrhea in all female patients receiving chlorpromazine (1). In those from 15 to 36 years of age receiving more than 200 mgms. of the drug daily, the incidence was 30 per cent.

Although no direct proof is available, it seems probable that both chlorpromazine and reserpine act primarily upon the hypothalamic centers influencing pituitary secretion. In the case presented, elevated urinary FSH levels were observed during reserpine induced lactation. Similar findings have been reported in patients exhibiting galactorrhea while being treated with chlorpromazine (11).

Extrinsic mechanical stimuli may also induce abnormal lactation. Slome describes three cases in Zulu grandmothers, one of them past the menopause, who successfully breast-fed their grandchildren (13). That this phenomenon is not restricted to women is revealed by Knott who, in his review, mentions several cases of active lactation in men subjected to suckling (14).

The flow of milk observed following herpes zoster of the chest (15), thoracotomy and thoracoplasty (16) has been ascribed to stimuli arising in injured sensory nerves which ordinarily innervate the nipples and act as receptors to the suckling stimulus. Among these cases, the one reported by Aufses is of unusual interest since he observed abnormal lactation in the remaining breast following radical mastectomy (17).

Among disturbances of the neuro-endocrine system producing abnormal lactation are psychiatric disorders, particularly schizophrenia (18); brain trauma, encephalitis, meningitis, tabes and syringomyelia (19-22); perisellar neoplasms (23); tumors of the pituitary (24); pineal tumors (25); endocrine tumors of the female and male (chorionepithelioma) gonads (26); adrenal tumors (27); menopause and castration (28); and dysfunction of the target organ, cystic disease of the breast (29).

Two syndromes with abnormal lactation as a predominant feature and evidence of pituitary dysfunction are sufficiently distinct to be placed in separate categories. The first is comprised of galactorrhea with amenorrhea, frequently associated with obesity, hirsutism and seborrhea, with low urinary FSH and slightly elevated 17 ketosteroids (30). Forbes and her coworkers found chromophobe adenomas of the pituitary in half of their patients with this disorder (31). The second is the Chiari-Frommel syndrome which occurs in post-partum, frequently asthenic and psychoneurotic women (32, 33). The clinical features include lactation persisting for months or years, uterine atrophy and amenorrhea. Low urinary FSH levels and low 17-ketosteroids have also been reported.

It is evident, even from a brief review of this nature, that the physician may

be confronted with abnormal lactation arising from a variety of causes. Historically, drug produced galactorrhea is the most recent however with the increasingly frequent use of reserpine and chlorpromazine-like drugs, it may become a relatively common form of abnormal lactation.

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NEUROPSYCHIATRIC PRESENTATION OF HYPERCALCEMIA

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Much has been written about the skeletal, renal and gastrointestinal manifestations of hypercalcemia, but relatively little emphasis has been focussed upon the neuropsychiatric symptomatology of this biochemical derangement. Regardless of the etiology of the hypercalcemia, confusion, lethargy and a bizarre organic mental syndrome may be the earliest manifestation. Recently, three patients were referred for neurological study because of severe mental changes. The presenting symptoms were those relating to the involvement of the nervous system. No definite diagnosis was made until a high serum calcium level was discovered. The case reports of these subjects follow.

CASE REPORTS

A 67 year old woman was admitted to The Mount Sinai Hospital for the first time with the chief complaint of confusion and mental deterioration. The patient was apparently well until December 23, 1956, when she was injured in an automobile accident. She sustained a fracture of the left wrist and had bruises and cuts on the left side of her head. There was no loss of consciousness. She was hospitalized at another hospital and x-rays of the skull were reported to be negative. She was discharged and remained well until January 27, 1957 when she began to show symptoms of nervous system dysfunction. Her gait became somewhat unsteady; she tottered from side to side when she walked. She became progressively more helpless and soon required a nurse to assist her with her personal hygiene. By March 1957 these symptoms were exaggerated and accompanied by severe loss of memory, disorientation and confusion. She became extremely dull and apathetic. There was marked bradyphrenia and bradykinesia. The patient just sat and had to be fed. The gait became extremely unsteady and she required support to get about. The family had noted an increased water intake, urinary frequency and subsequent incontinence. Various consultants suggested that the patient had cerebral arteriosclerosis and that she be institutionalized in a psychiatric hospital. Since cerebral arteriosclerosis rarely causes such severe mental deterioration within a three month period, the patient was finally advised to have a complete examination prior to such commitment.

The physical examination on admission was essentially negative, except for slight enlargement of the heart. On neurological examination the chief findings were mental changes characterized by disorientation, confusion and marked lapse of memory. There were no gross motor deficits, abnormal tendon or pathological reflexes. Coordination was generally poor. The gait was unsteady.

Laboratory findings on admission revealed the hemogram to be within normal limits. The urine showed a specific gravity of 1.015 with a faint trace of albumin, 15 RBC/HPF and 15 to 20 WBC/HPF. Blood urea nitrogen was 6 mg % and the fasting blood sugar level was 124 mg %. The lumbar puncture revealed a normal pressure and the cerebrospinal fluid

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contained four lymphocytes per cubic mm and a protein of 47 mg %. The sedimentation rate was 8 mm/hr. Skull x-rays revealed some thinning of the dorsum sellae and posterior clinoids. There was an irregular, rounded calcification in the left posterior frontal region slightly to the left of the midline, and two small calcifications posteriorly which were interpreted as being the choroid plexuses. A pneumoencephalogram revealed slightly dilated, lateral and third ventricles without displacement.

Following the pneumoencephalogram, the patient had a mild headache but otherwise felt well. She continued to be extremely apathetic, markedly confused and disoriented. She was incontinent of urine. Over the succeeding week the patient's state of consciousness continued to fluctuate and her obtundation continued to increase. There were gross twitchings of the hands and fingers. Of interest was the frequent, sudden, temporary drop of the outstretched hands appearing not unlike myoclonic jerks. There was also a tendency to suddenly relax her grip, on a spoon for example, but this was immediately compensated for. Because of the marked fluctuation in the patient's state of consciousness, it was thought that a subdural hematoma might be present. On March 9, 1957 a left carotid arteriogram was performed which showed good visualization of the carotid syphon and anterior and middle cerebral arteries without displacement or abnormality.

Since the patient's depressed mental status continued, complete work-up was undertaken. Her basal metabolic rate was minus 9%. Electroencephalograms on several occasions were abnormal with diffuse slowing and shifting bursts without evidence of a cortical focus. Radioactive iodine uptake by the thyroid gland was 30% in 24 hours. The serum calcium concentration was found to be 15.8 mg %, the phosphorus 1.9 mg %, the sodium 145 meq/L, potassium 3.6 meq/L, chloride 102 meq/L, alkaline phosphatase 9.3 KA units, and uric acid 8.9 mg %. Repeat blood chemistries revealed the uric acid concentration to be 7.2 mg %, calcium 15.2 mg % and phosphorus 1.7 mg %. The endogenous creatinine clearance was 40 ml/minute.

Subsequently, x-ray examination of the long bones, pelvis and hands showed considerable demineralization. There was a healing fracture in the upper end of the right fibula and in the distal end of the left radius. The appearance was thought to be consistent with, though not pathognomonic of, hyperparathyroidism. An intravenous pyelogram showed prompt excretion bilaterally without any evidence of opaque concretions in the kidney contours. There were some rounded calcifications in the pelvis classified as "undoubtedly phleboliths".

Upon careful cross examination of the family, it was determined that for the past five to six years the patient had been taking a medication containing 100,000 units of vitamin D as well as other vitamins daily without prescription. In addition, the patient had been eating large quantities of sour cream. From this it was concluded that the clinical picture and the laboratory findings could be explained by the toxic metabolic disorder of serum hypercalcemia secondary to hyper-vitaminosis D and an increased calcium intake.

The patient was consequently placed on a low calcium diet. During the succeeding two weeks the patient became much brighter and more responsive. The blood calcium level dropped to 14.0 mg %. Her mental status improved and she became more interested in her environment. She began to feed herself and was able to carry on a good conversation with her family and physicians. Following her discharge from the hospital, she has continued to improve, and has remained well.

On three month follow-up examination, her calcium level had fallen to 12.0 mg % and she was almost asymptomatic with virtually a complete subsidence of the organic mental syndrome.

A 62 year old woman was admitted to The Mount Sinai Hospital for the first time on October 1, 1957 with the chief complaint of personality change and epigastric discomfort. At that time she said that she had enjoyed perfect health until three weeks before admission when she experienced a brief bout of sharp epigastric pain. Subsequently she had repeated episodes of vomiting, frequent loose bowel movements, and loss of appetite. She also com-

plained that "her whole personality had changed". There was no previous history of serious illness and system review revealed no significant symptomatology.

The physical examination was entirely normal. Routine examination of the urine showed a faint trace of albumin, a specific gravity of 1.019, 3 to 5 RBC/HPF and 15 to 20 WBC/HPF. The hemoglobin was 12.0 gm % and the white blood count was normal. The sedimentation rate was 33 mm/hour, the blood urea nitrogen 17 mg %, and the fasting blood sugar level 91 mg %. Alkaline phosphatase was 14.6 KA units, the serum amylase 32 units, sodium 139 meq/L, potassium 4.0 meq/L, and chloride 101 meq/L. Radiological studies of the chest and abdomen revealed no abnormalities. Barium enema and intravenous pyelogram were normal.

After her discharge from the hospital on October 9, 1957, the patient continued to vomit frequently, usually right after her meals. These episodes were followed by severe occipital headaches which diminished in intensity over the subsequent hours and were unaccompanied by any other symptoms. Occasionally these occurred without prior vomiting. She was therefore re-admitted on November 8, 1957. Physical examination was again within normal limits. A routine blood count and urine examination on admission were normal. The blood calcium level was 13.3 mg % and the alkaline phosphatase 14.2 KA units. On her second hospital day, immediately following an episode of vomiting, the patient was found to have an irregular tachycardia of 120/min. An electrocardiogram showed the presence of atrial fibrillation. This remitted spontaneously and a subsequent ECG was normal. Repeat radiologic studies of the gastrointestinal tract were normal as was a sternal marrow examination.

On the third hospital day, the patient became confused and disoriented. On neurological examination she confabulated having been to Japan during the previous night. She tended to perseverate and had difficulty in calculation. Occasionally she confused right and left. The face-hand test (bilateral simultaneous stimulation of face and hand) showed displacement from either hand to the face. Instead of reporting the sensation in one hand and in the face, she indicated that the stimuli were applied to either side of the face. There was generalized weakness. The outstretched left upper extremity fell in a jerky fashion which the patient claimed she could not control. There were no ataxia or tremors. The reflexes were equal and active throughout and there were no pathological reflexes. The cranial nerve and sensory examinations revealed no defects. Slight resistance to flexion of the neck was noted.

A lumbar puncture showed faintly turbid, colorless fluid under an initial pressure of 15 cm H₂O which contained 6 lymphocytes and 550 fresh RBC/cu mm and a protein of 20 mg %. An electroencephalogram showed diffuse bursts of 2 to 4 cps activity, most marked anteriorly, which increased on hyperventilation.

Over the course of the next ten days, the patient showed marked fluctuation in her mental status. The remainder of the neurological picture was unchanged. She continued to suffer from severe nausea and vomiting which frequently necessitated intravenous fluid therapy to maintain hydration. She was placed on a Bauer-Aub low calcium diet. The serum calcium fluctuated between 10.9 and 14.5 mg % and the phosphorus between 2.8 and 4.1 mg %. A 24 hour urine specimen of 2600 ml contained 432 mg of calcium and 403 mg of phosphorus. From the 12th hospital day on, the patient became progressively more lethargic and disoriented and on the 16th day became comatose, responding only to painful stimuli. There was resistance to flexion of the neck. The reflexes were equal and the fundi were normal. Occasional myoclonic movements of the right side of the face and right shoulder were described. The blood calcium on that day was 14.5 mg %, the phosphorus 3.9 mg % and the plasma creatinine 1.2 mg %. Over the course of the subsequent two days there was gradual deepening of the coma and the patient appeared pre-terminal.

On the 18th hospital day, an exploration of the neck was performed on the chance that a parathyroid adenoma might be found. However, the pathologist could report only normal thymic, thyroid and parathyroid tissue in the specimens which were removed. The patient ceased on the day following operation.

Post-mortem examination revealed an area of focal adenomatous hyperplasia, 2 mm in diameter, in one remaining parathyroid gland. No other evidence of parathyroid tissue was found in the neck or mediastinum. In addition, multiple pulmonary emboli with a right lower lobe pulmonary infarct, and left lower lobe atelectasis secondary to a mucopurulent plug in the left lower lobe bronchus were found. A healed duodenal ulcer and a sessile adenocarcinoma of the rectum without evidence of regional or distant metastases were also present. In the bones examined, there was no evidence of osteoclastic activity destruction. Examination of the brain revealed no abnormalities.

This case has already been reported at length elsewhere (13). This 48 year old widow was in excellent health until July 1954, at which time she became progressively listless and withdrawn. She noted pain and swelling of her left knee which was treated by her physician with "vitamins" and injections. Over the course of the succeeding two months, she became increasingly drowsy and, by the second week in October, spent most of her time asleep.

On October 13, 1954, she was admitted to The Mount Sinai Hospital, where general examination revealed only a small node in the left axilla and a vague abdominal mass.

On neurological examination, she was disoriented in all spheres, she perseverated, and was grossly out of contact. The reflexes were hypoactive but the remainder of the examination revealed no abnormalities.

Roentgenological examination showed no significant abnormalities in the skull, chest, long bones or urinary system. Lumbar puncture was normal. The EEG revealed diffuse, symmetrical 4 to 6 cps activity with high voltage 1.5 to 2 cps bursts. The blood urea nitrogen was 54 mg %, creatinine 2.9 mg %, and phosphorus 4.4 mg %.

It was only after the finding of the elevated blood calcium, that the history was elicited from the patient's physician that she had been taking 100,000 units of Vitamin D daily for six weeks during July and August of 1954.

On a low calcium diet, the blood urea nitrogen decreased to 24 mg % and calcium to 12.5 mg %. Concurrently, the patient became less drowsy and less obtunded. She was discharged on October 30, 1954, remarkably improved.

The patient continued to do well after discharge until three weeks before the second admission on December 29th, when the lethargy had returned and was accompanied by anorexia, constipation, weight loss and pain in the left shoulder. On physical examination, the woman appeared chronically ill and lethargic. An irregular, freely movable mass, 3 by 7 cm, was noted in the left axilla and a rubbery lymph node, 2 by 3 cm, was felt in the right supraclavicular area. The liver edge was palpable one fingerbreadth below the right costal margin and a previously described mass in the left upper quadrant had increased in size. There was tenderness over the lower cervical and upper thoracic vertebrae. Neurologic examination revealed marked lethargy and obtundation. When rousable, the patient was disoriented for time and place.

The blood urea nitrogen was 25 mg % and the ESR 91 mm/hr. The hemoglobin was 10.5 gm %, the WBC was 9,700 per cu mm, with 51% neutrophils, 24% lymphocytes, 20% mononuclear cells and 5% eosinophiles. Platelet and reticulocyte counts were normal. The serum calcium was 17.4 mg %, serum phosphorus 3.1 mg %, and the alkaline phosphatase was 9.8 KA units. X-ray studies of the cervical and dorsal spine and of the left shoulder revealed no abnormality. A plain film of the abdomen showed the outline of the left kidney to be obscured. On the second hospital day, a biopsy of the mass in the left axilla was performed and the diagnosis of Hodgkin's Disease in lymph node tissue was reported by the pathologist.

The patient remained afebrile but the obtundation and lethargy continued for the first three hospital weeks. On the sixth hospital day, ACTH, 60 units per day, was begun, and on the tenth day, cortisone, 100 mg per day was substituted. At the same time, radiotherapy was given to the left axilla, left upper quadrant of the abdomen, and the right cervical region. The patient's lethargy and confusion gradually cleared. By the 26th hospital day, the serum calcium level had fallen to 10.1 mg %, the serum phosphorus to 1.9 mg %, and the blood urea nitrogen to 19 mg %. The patient was discharged on February 4, 1955. At

that time, the masses in the abdomen and left axilla had decreased in size, but new lymph nodes were noted in the left cervical region.

The patient was well for a few weeks after discharge, but then became febrile. Nitrogen mustard therapy was administered at home, after which thrombocytopenia and leucopenia developed. She died suddenly two months after discharge with evidence of central nervous system bleeding. No post-mortem examination was performed.

DISCUSSION

The majority of the currently popular texts of medicine, endocrinology and neurology do not emphasize the changes in mental status or consciousness in patients with hypercalcemia nor do they stress that such changes may provide the predominant presenting symptoms. However, sporadic reference has been made to involvement of the nervous system in such patients in the literature of the past two decades. Fitz and Hallman, as recently as 1952, were the first to call attention to the fact, in the American literature, that hyperparathyroid patients may present with mental symptoms which clear after surgical removal of the parathyroid adenoma (1). Bartter, in his excellent review on the parathyroid gland and its relation to the nervous system, lists among other symptoms of hypercalcemia: psychosis, depression, listlessness, lethargy, apathy, drowsiness, fatigability and mental retardation as well as weakness, hyperreflexia and hyposensitivity to sensory stimuli (2). Eitinger calls attention to the fact that seven out of the fifty patients he studied with hyperparathyroidism, showed mental changes (3). Other authors mention neuropsychiatric symptoms in hyperparathyroidism, in vitamin D intoxication, and in hypercalcemia associated with androgenic and estrogenic therapy (4-7). Finally, Wenger *et al.*, in reviewing the symptoms of hypercalcemia in the milk-alkali syndrome states: "... mental confusion, ataxia, stupor and toxic psychosis may dominate the picture" (8).

The three patients presented here demonstrate the difficulties in diagnosis when the primary and most conspicuous manifestation of hypercalcemia relates to the central nervous system. As is summarized in Table I, mental changes of varying duration and progressive nature were the prominent presenting complaints in all three cases. In each instance, primary brain disease was suspected, because no obvious cause for the symptomatology was in evidence and neurological consultation was therefore requested. In the first case, the picture was further confused by the history of recent cerebral trauma and therefore the possibility of subdural hematoma was seriously considered. After all studies had failed to demonstrate any evidence of a space-occupying intracranial mass, a complete spectrum of blood chemistries revealed the presence of hypercalcemia. The history of high vitamin D and calcium intake was obtained only after meticulous questioning of the patient's family. In the second patient, the course was extremely rapid and progressive. Despite a rather careful search of the mediastinum at the time of post-mortem examination, no satisfactory cause for the hypercalcemia could be found, except for the small area of adenomatous change in the remaining parathyroid. However, primary hyperparathyroidism remains as the most probable diagnosis.

It is interesting to note that both the first and second patients showed sudden,

TABLE I

Age	Sex	Neurological Presenting Symptoms	Duration	Admission Blood Chemistries				E E G	Etiology
				Ca mg. %	P mg. %	Alk Phase K.A.U.	Urea N mg. %		
67	♀	Mental retardation, lassitude, dyscalculia, disorientation, unsteadiness, muscular weakness, polydipsia, anorexia	5 weeks	15.8	1.9	9.3	12	Diffuse 4-6 cps, shifting bursts 1.5-3 cps	Hypervitaminosis D
62	♀	Personality change, nausea, anorexia	9 weeks						
		Confusion, disorientation, dyscalculia, weakness	3 weeks	13.3	2.3	14.2	12	Diffuse bursts 2-4 cps	Possible hyperparathyroidism
48	♀	Progressively deepening coma	1 week	14.5	3.9			Diffuse 4.6 cps	
		Listlessness, fatigue, drowsiness, confusion, perseveration, disorientation, blurring of vision	3 months	13.8	4.1	10.2	60	Diffuse bursts 1.5-2 cps	
		Lassitude and drowsiness	2 months later	17.4	3.1	9.8	26		Hypervitaminosis D Hodgkins disease

fleeting loss of tone in outstretched extremities which gave the appearance of jerky, almost myoclonic dropping of the limb which was immediately restored to its original position. This symptom was quite prominent. Patients who manifest such symptoms should be suspected of some form of intoxication.

All three patients showed moderate, diffuse slowing in their electroencephalograms; this was accompanied by diffuse bursts of 1.5 to 2.5 cps activity. This type of disturbance is also non-specific and can be seen in cerebral dysfunction due to a wide variety of etiologies (9).

The organic mental syndrome, as described in the literature and displayed by the patients presented, cannot be characterized in any specific manner, except that it is usually accompanied by marked lassitude and drowsiness, occasionally stupor and coma. The patient is often disoriented and confused, has a poor memory, has difficulty in calculating and has a short attention span. The face-hand test is usually positive (10). Incontinence of urine and feces and difficulty in personal hygiene are frequently noted. Such mental changes are characteristic of any type of diffuse cerebral dysfunction. Consequently, diagnoses of brain damage due to pressure of intracranial tumor, subdural hematoma, or hemorrhage are entertained. When these symptoms are accompanied by anorexia, nausea, vomiting, epigastric pain, muscular weakness, constipation or polydipsia and polyuria, hypercalcemia as an etiologic factor should be strongly suspected. However, the possibility of a hypercalcemic syndrome should be borne in mind in the diagnostic evaluation of all patients with organic mental syndromes of obscure etiology.

Prolonged hypercalcemia may cause parenchymatous and tubular deposition

of calcium in the kidneys. Thus pyelonephritis with consequent reduction in renal function may ensue. Furthermore, abrupt elevation of the serum calcium level causes immediate alterations of tubular function such as reduced tubular reabsorption of salt and water (11). The salt and water losses due to the consequent polyuria may cause dehydration and further reduction, albeit reversible, in renal function (12). In prolonged hypercalcemia, irreversible renal damage may be produced. Generally, as renal function falls consequent to hypercalcemia, the level of the serum calcium rises precipitously. However, a fall in renal function may cause an elevation of the serum phosphorus with a consequent reduction in the serum calcium, sometimes obscuring to some degree, the original hypercalcemia. Since, in many cases, the pathologic state causing the hypercalcemia may be correctible, the importance of prompt recognition of this condition by determination of the serum calcium level is self-evident.

The following pathologic entities may produce hypercalcemia:

(a) Hypervitaminosis D; usually after intakes in excess of 100,000 units per day for prolonged periods (5, 6).

(b) Hyperparathyroidism (1, 3, 4).

(c) The milk-alkali syndrome; high dietary calcium content, especially when accompanied by insoluble alkali. This entity is most frequently encountered in patients treated for duodenal or gastric ulcer (8).

(d) Boeck's sarcoid.

(e) Hodgkin's disease (11).

(f) Estrogen or testosterone administration in large doses for extended periods (7).

(g) Metastatic malignancy involving bone.

(h) Multiple myeloma.

(i) Prolonged immobilization.

The precise mechanisms by which alterations in the serum calcium level produce functional changes in the intact central nervous system are not clear. There is a considerable body of experimental data which indicates that elevation of calcium above physiologic levels can produce profound alterations in nerve function, both peripheral and central (14, 15). These include: increased threshold to electrical stimulation of myelinated nerve fibers (16-18); decreased rate of discharge of the post-synaptic neuron in the sympathetic ganglia where the discharge is produced either by administration of acetyl choline or tetanic stimulation by way of the presynaptic fiber (18); acceleration of the decrease in successive end plate potentials during repetitive stimulation of the neuro-muscular junction via the motor nerve (19). It has been found that increasing the calcium concentration of the perfusing medium causes a decrease in permeability of the nerve membrane to ions and this has been offered as a possible explanation of the alterations in the electrical properties (20). Also in brain slices, calcium tends to depress respiration (21).

SUMMARY

Not infrequently a patient may present with confusion, lethargy and a bizarre organic mental syndrome as the primary expression of hypercalcemia, regardless

of etiology. Three cases are reported which were referred for neurological consultation because of a peculiar organic mental syndrome, a clinical picture which caused much diagnostic confusion until a high serum calcium level was established as the etiological factor. In two of the patients, fluctuations in the serum calcium levels were observed to be correlated with changes in mental status; confusion increasing with the rise in the serum calcium level. The underlying causes for the hypercalcemia were Hypervitaminosis D, Hodgkin's Disease and parathyroid adenoma in the three patients respectively. It is emphasized that neuropsychiatric symptomatology may be the presenting picture of a hypercalcemic syndrome. Since prolonged hypercalcemia may cause severe renal tubular damage and even death, and since, in many cases therapeutic measures are available for eliminating either the primary cause of the hypercalcemia or lowering the serum calcium level (e.g. by ethylene diamine tetraacetic acid), early diagnosis is extremely important. The possibility of hypercalcemia should therefore be borne in mind in the differential diagnosis of organic mental syndrome of obscure etiology.

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REGIONAL ENTERITIS PRESENTING AS GROSS RECTAL BLEEDING

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The purpose of this paper is to emphasize the need for including regional enteritis in the differential diagnosis of gross rectal bleeding. Gross rectal bleeding includes blood streaked stools, melena, (tarry stools), and profuse hemorrhage per-rectum.

Gross rectal bleeding can occur as the predominant or only presenting symptom of regional enteritis. Fever, fistuli, diarrhea, and severe abdominal pain do not need to be present. The case to be presented bears witness to this fact.

Fallis first reported a case of regional enteritis with gross rectal bleeding as the presenting symptom in 1940 (1). His patient had profuse bleeding over a seven week period which required eight transfusions. Regional enteritis was discovered by exploratory laparotomy. Yunch and Crohn reported their first case of regional enteritis ushered in by gross bleeding in 1941, and they considered this to be very atypical (2). In 1958 Crohn and Yarnis reporting on 542 patients, were able to add only one more case of this nature (3). The total incidence of their series was only .37 per cent. In 1957 Brown described a case of unexplained rectal bleeding due to regional enteritis, and emphasized the need to consider that condition as a cause of rectal bleeding.

CASE HISTORY

A 65 year old white female was admitted to The Mount Sinai Hospital on December 15, 1958. She presented with a two year history of intermittent gross rectal bleeding. This was described as the passage of stool surrounded by a string of red blood. She also complained of intermittent, mid-abdominal cramps which often terminated after the passage of dark red clotted blood which was the consistency of jello. The bleeding and cramps became more frequent over the two year period. There was no history of diarrhea, constipation, nausea, or vomiting. Ten months prior to admission the patient had one episode of fever (104°F.) and erythema nodosa. This was treated with triamecinolone, and both the fever and erythema disappeared. The patient was still taking triamecinolone in low dosage at the time of admission.

Gastrointestinal x-rays and sigmoidoscopy done in her home town were considered to be negative. A barium enema examination just prior to admission* revealed a large polypoid lesion in the mid-sigmoid colon. It was assumed that this was the main cause of the gross rectal bleeding. Accordingly, excision of the polypoid lesion was entertained.

Physical examination revealed a well developed, well nourished white female who showed no signs of acute or chronic disease. There was mild, generalized abdominal tenderness, but no other significant physical findings.

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The laboratory findings were as follows: Hemoglobin, 13.3 gm per cent; wbc, 8,550/cu mm; platelets, 262,000/cu mm. Clotting and bleeding times were normal. The stool was brown and semiformed; the guaiac was 2 plus.

Operation was performed on December 18, 1958. A broad based, partially soft, partially indurated, polypoid lesion, three centimeters in diameter, was found in the mid-sigmoid colon. Careful examination of the rest of the bowel revealed nothing but some thickening of the distal two feet of ileum. This was not deemed to be of importance. The polypoid lesion was removed together with a small segment of adjoining colon (Fig. 1). There was no ulceration and no evidence of active bleeding from the polyp. Frozen section revealed adenocarcinoma with no infiltration at the base. A left hemi-colectomy and aortic node dissection (with an incidental splenectomy) were performed. The distal ileum was re-examined just before closing the abdomen and the thickened ileum appeared to be unchanged. Since pathology sufficient to explain the bleeding was found, the abdomen was closed. The final pathology examination revealed no metastatic lesions in the sixteen regional nodes.

Post-operatively, the patient did well for six days. She then began to pass large amounts of blood from the rectum and required two transfusions. The profuse bleeding subsided spontaneously, however, stool guaiac tests continued to be positive. On the twentieth post-operative day there was fever of 103°F. and symptoms of intestinal obstruction. The latter gradually subsided, but she continued to have fever in the range of 100° to 101°F. until given steroid therapy. This had been gradually discontinued post-operatively. On February 2, 1959 a barium meal was given. X-rays revealed a loop of small bowel, measuring ten to twelve inches long which lacked mucosal pattern and serrated margins (Fig. 2). The terminal six inches of ileum appeared to be normal. A diagnosis of regional enteritis was made. The patient was discharged on February 5, 1959 on conservative therapy which included Prednisone®. It was felt that in light of a mild coronary occlusion, which she sustained during her hospital course, operation should be temporarily postponed. On February 9, 1959, four days after discharge, the patient was readmitted to the hospital after having two episodes of severe rectal bleeding. She appeared pale and ill. Her hemoglobin was 8.3 gm per cent. Blood was easily visible in the stool. She received five units of blood. Operation was performed on February 11, 1959. Ten inches of thickened, red, edematous, small bowel was found approximately six inches from the ileo-cecal valve. An ileo-ascending colostomy and resection of the involved ileum was performed. The resected ileum was diagnosed as chronic and acute regional enteritis with multiple skip areas and marked narrowing of the lumen. There were many scattered ulcerations.

The post-operative course was rather stormy and was complicated by a perforated cecum which was exteriorized and closed at a later date. At present, the patient has no rectal bleeding, no fever, and no abdominal complaints.

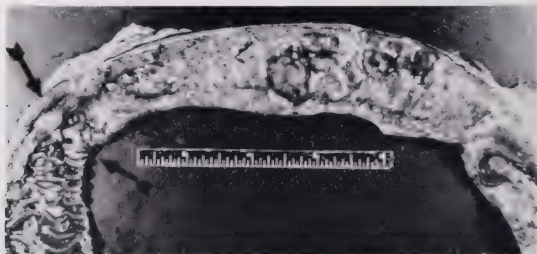


FIG. 1. Gross specimen of resected ileum. Arrows separate normal intestine on left (with distinct plicae circularis) from diseased intestine (loss of plicae with scarring and inflammation of mucosa) on right.

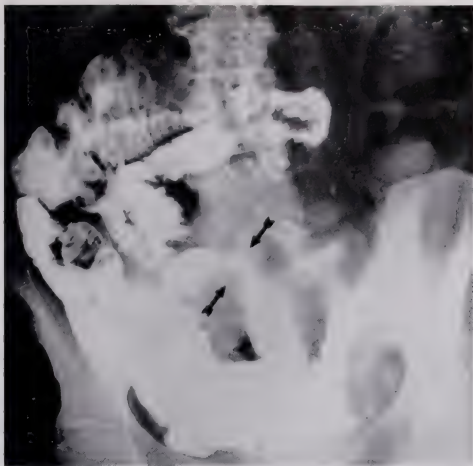


FIG. 2. Small bowel study of patient taken on 2/2/59. Ileum between arrows shows loss of mucosal pattern and serrated margins. "Rigid" configuration persisted on all films.

DISCUSSION

This case history points up the necessity of keeping regional enteritis in mind when presented with relatively asymptomatic gross rectal bleeding. It also points up the necessity of doing a complete gastrointestinal study even though a plausible lesion is found in the first one.

Gross rectal bleeding, when considered as a concomitant of other more typical symptoms of regional enteritis, and not as the sole presenting complaint, is not rare. Van Potter reported a history of gross rectal bleeding in 88 (16%) of 504 patients at their initial visit (5). Sixty or ten per cent of the total cases had blood streaked stools, and 16 or six per cent had profuse bleeding or melena. Daffner and Brown reporting on one-hundred cases, found 24 per cent with blood streaked stools, and ten per cent with profuse bleeding or melena (6). Crohn and Yarnis reporting only profuse bleeding and melena, found 25 cases out of a total of 542 cases or 4.5 per cent (3). Considering the amount of inflammation and ulceration, it is surprising that the incidence of gross rectal bleeding is not much higher. This can probably be attributed to the shallowness and narrowness of the ulcerations. Schenken and Binns in describing the gross pathologic findings state that it is only with the help of a dissecting loop that numerous shallow, fissure-like ulcerations are noted (7). Furthermore, the ulcerations do not usually extend beyond the muscularis mucosa. The ulcerations that do go beyond, often form fistuli because of their narrowness, have a low probability of striking one of the larger vessels, which, in the small intestine, typically lie in the submucosa.

French's Index of Differential Diagnosis lists 57 causes of gross rectal bleeding and curiously fails to mention regional enteritis (8). When probably 65 to 75 per cent of gross rectal bleeding can be attributed to peptic ulcers and another 10 to 15 per cent to esophageal varices and neoplasm, regional enteritis is certainly not common; nevertheless it should be considered as a potential cause.

SUMMARY

A. Gross rectal bleeding, as in the case presented, may be the only, or pre-dominant presenting symptom of regional enteritis.

B. Gross rectal bleeding as a concomitant symptom of regional enteritis occurs in approximately 16 to 24 per cent of cases. Severe bleeding and melena (excluding blood streaked stools) can be expected in 4 to 6 per cent.

C. The reason for the comparatively low incidence of gross rectal bleeding in regional enteritis may possibly be explained by the shallowness, and more important by the narrowness of the ulcerations.

D. Consideration must be given to regional enteritis as a cause of gross rectal bleeding.

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ACTINOMYCOSIS WITH CEREBRAL AND PROBABLE ENDOCARDIAL INVOLVEMENT

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Actinomycosis although not an extremely rare disease, is uncommon. Concomitant involvement of the abdominal organs, endocardium, and central nervous system is rare. It is our purpose to report a case of actinomycotic disease of the central nervous system, and its successful treatment.

CASE REPORT

A 64 year old male, was admitted to The Mount Sinai Hospital with the complaints of weakness, anorexia, severe anemia and a right upper quadrant mass of two months duration. He had suffered an injury to the lower region of the back in an automobile accident three years before admission. Significant past history included a brief episode of chest pain which occurred two years before admission and which was relieved by injection of an opiate. He had recurrent sore throats presumably due to inflamed tonsils, (going back for many years) and on one occasion he was told that he had a possible small stone in his left submaxillary gland.

He had been in relatively good health until about six weeks before admission when he began to experience increasing fatigue, malaise, anorexia and occasional chilly sensations. Two weeks after the onset of these symptoms he was treated with erythromycin, but with no improvement. Physical examination revealed guarding, and a probable mass in the right upper quadrant. A series of studies such as abdominal x-rays, cystoscopy, upper gastrointestinal barium contrast x-rays, cholecystogram and barium enema x-ray were reported as negative. The blood showed a moderately severe anemia, while urinalysis revealed microscopic hematuria. Because of continuing anorexia, anemia, a right upper quadrant mass, and weight loss, he was admitted to the hospital October 30, 1956.

He presented with marked pallor but appeared well nourished. The blood pressure was 126/80 mm Hg, temperature 101°F and the pulse rate 100. Examination of the head and neck were unremarkable. The left ear drum was scarred and hearing was markedly impaired on the left side. The tonsils were small and reddened and the crypts contained some debris and secretions. There was no significant lymph node enlargement. The left border of the heart was percussed two cm to the left of the mid-clavicular line. There was a grade I systolic murmur over the aortic area and a grade II apical systolic murmur. Occasional scattered sibilant rales were heard over both posterior lung fields. Examination of the abdomen revealed a sense of resistance in the right upper quadrant with the liver edge felt one fingerbreadth below the costal margin. A definite mass could not be felt although there was a suggestion of one in or under the liver. Rectal examination revealed an enlarged soft prostate. The peripheral pulses were present and neurological examination was normal.

Laboratory studies, done at the time of admission, revealed the hemoglobin to be 7.3 gm %, white cell count 3,400 per cu mm, a differential count of 60% polymorphonuclear neutrophils, 11% band form neutrophils, 20% lymphocytes, 2% monocytes, 6% atypical lymphocytes, and 1% metamyelocytes. Red cell anisocytosis and hyperchromasia were

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noted on the smear. Urine specific gravity was 1.022 without albumin or sugar and the sediment contained 5 to 6 WBC/HPF. Sedimentation rate was 99 mm/hr (Westergren).

The blood urea nitrogen was 16 mg %, blood sugar 122 mg %, alkaline phosphatase 5.2 KA units, serum proteins 7.4 gm % with serum albumin 3.1 gm % and serum globulin 4.3 gm %. The Bromsulfalein retention was 3.5% in 45 minutes. Bilirubin was 0.87 mg % total with 0.13 mg % indirect. The blood Wassermann was negative. The stool was negative for ova and parasites. There was no Bence-Jones protein in the urine. Three blood cultures showed no growth. Blood smears were negative for malarial parasites and agglutinations for salmonella, brucella and shigella organisms were negative. Two lupus preparations were negative. Circulation time was 20 seconds (Decholin®). Sternal marrow studies revealed 24% myelocytes, 0.3% myeloblasts, 1% eosinophilic myelocytes, 23% segmental neutrophils, 1.5% hemotogones, 0.2% reticulum cells, 3.0% erythroblasts, 34.0% normoblasts; the megakaryocytes were plentiful. The platelet count was 240,000 per cu mm, and the hematocrit 25%. The marrow, restudied one week later, appeared closer to normal but similar to the previous examination.

Electrocardiographic tracings showed changes suggestive of an old diaphragmatic wall myocardial infarction, and left ventricular hypertrophy.

X-ray studies revealed a normal excretory urogram, skull, and long bones. The dorso-lumbar spine showed marked arthritic changes, particularly in the lower lumbar region. A chest x-ray demonstrated a slight transverse enlargement of the heart, and a tortuous and elongated aorta. There was no abnormality of the lung parenchyma.

Special serum microprotein studies revealed a high gamma globulin.

During the first two weeks there were temperature elevations to 101°F nearly every day and the murmurs became grade II to grade III in intensity. The clinical impression of sub-acute bacterial endocarditis was entertained. Prior to the advent of therapy, 14 days after admission, he was found to be disoriented, with a marked expressive aphasia, and a positive face-hand test. Further examination disclosed a right homonymous field defect, right hemiparesis, right hemi-hypalgesia, and a right Babinski sign. The findings pointed to a left central lesion. Accordingly, a lumbar puncture was done. The pressure was normal but the fluid was turbid, yellow, and contained 87 polymorphonuclear and three mononuclear cells per cubic millimeter. An electro-encephalogram was severely abnormal and consistent with diffuse cerebral dysfunction in the presence of an extensive or deep left sided lesion.

The temperature began spiking to 104°F and the patient's condition became more critical. Although blood cultures were negative, antibiotic therapy was begun immediately. Six days later *Actinomyces bovis* was reported from the spinal fluid culture. The organism was sensitive to penicillin, tetracycline, and chloramphenicol *in vitro*.

The patient's condition improved, and by the end of one week, no neurological abnormality could be detected except for a slight sensory defect. The mass in the right upper quadrant became less prominent and was barely palpable. Two weeks after onset of therapy, the spinal fluid contained seven cells per cu mm, four polymorphs and three mononuclears and a protein of 35 mg %.

During the first two weeks the patient was treated with digoxin and Diamox®. After blood and marrow studies were concluded he was given four units of blood. The hemoglobin rose to 11 gm %. With the advent of cerebral complications, tetracycline, 200 mg was given intramuscularly and then 500 mg was given every six hours. Because of a history of penicillin sensitivity, he was started on 200 units of sodium penicillin G, given slowly in infusion of normal saline.* Since there was no reaction to this and then gradually higher dosages, the dosage was increased to 10 million units a day. Gantrisin® in the dosage of 4 gm a day was added. After one week the penicillin administration was changed to the intramuscular route and the dosage administered was six million units per day. This antibiotic therapy was continued for four weeks. His subsequent course was uneventful and he made a full recovery.

* Penicillin "desensitization" was done by Dr. Eli Pearlman.

DISCUSSION

Actinomycotic infection in man was reported by Israel as early as 1878 (1). Israel, Wolff and others established that *Actinomyces* is a frequent inhabitant of the oral cavity and respiratory tract so that infection in man may be endogenous (2). With the disruption of normal barriers to infection, penetration of the mucous membranes of the respiratory and alimentary tract or of the skin may occur (3). Infection may be superimposed upon trauma or other predisposing factors such as acute diverticulitis. Later, Harvey, Cantrell, and Fisher reported four cases resulting from perforation of the intestinal tract due to fish bones (4).

Cornell and Shookhoff reviewed 68 cases of cardiac actinomycosis and found involvement of the heart by direct extension in 29, pyemic involvement from distant foci in 19, pericarditis from adjacent structures in 12; the cause was not clear in five cases (5). Clinical evidence of heart disease was found in only 23 of 60 patients who exhibited congestive heart failure. The majority of these 23 patients showed large pericardial accumulations. Zoeckler also reported pericarditis by extension from the chest wall and stated that hematogenous spread may result in myocardial involvement before the pericardium or endocardium are involved (6).

Although the cervicofacial connective tissues have been thought to be the most common source of primary actinomycotic infection, a recent, 25 year review of 37 cases from the Johns Hopkins Hospital gives the incidence of primary sites as abdominal 63 per cent, cervicofacial 24 per cent and pulmonary 13 per cent. Where secondary spread occurred it involved the abdominal wall of viscera in 55 per cent, thorax in 23 per cent, cervicofacial tissue in 13 per cent, and brain or meninges in 6 per cent (4).

Urh reported two cases of endocardial actinomycosis (7). The first was a twenty-four year old man who had a febrile illness lasting twenty five days with findings of a soft apical systolic murmur, dullness over the right lower lobe of the lung, blood streaked sputum, right upper quadrant tenderness, and petechiae. *Actinomyces bovis*, micro-aerophilic type requiring reduced oxygen tension for growth was isolated from the blood, from valvular vegetations and from infarcts of the lungs, spleen and kidneys. He had received treatment with sodium iodide. The second case was a seventy-one year old woman who at autopsy was found to have nodules on the aortic and mitral valve from which *Actinomyces* was grown on culture.

Wedding reported cases with fever and murmurs, which were temporarily controlled by sulfathiazole (8). In one of these cases there was a pleocytosis and an elevated protein concentration in the spinal fluid. At post mortem examination there were valvular vegetations, a large occipital lobe abscess and focal microscopic abscesses in the cortex. Septic infarcts were also found in the spleen, liver and intestine.

McNeal, Blevens, and Duryea reported a case of a mitral valve with positive blood cultures, emboli, aphasia, hemiplegia and amnesia. Recovery followed treatment with intravenous penicillin over a nine month period (9). Cope re-

ported six patients with abdominal actinomycosis five of whom were originally suspected of having a malignant lesion (10).

Ordinarily in cases of actinomycosis there is a slight to moderate anemia, an elevated sedimentation rate, and a moderate leucocytosis. Cultures under anaerobic conditions give rise to a branching filamentous organism. The growth is slow with pinpoint greyish brown soft colonies appearing in five days. Under the microscope are seen variable cocci and rods, many basophilic which later become branching filamentous mycelia and small granules. Growth is best accomplished on Brewer's Thioglycollate or anerobic blood agar. Search should be made for sulfur granules in all draining sinuses.

Treatment is often difficult because the involved areas are extensive, often avascular, and therefore require intensive and prolonged anti-microbial therapy as well as surgical excision (11, 12).

In 1948 penicillin therapy for actinomycosis was firmly established. In 1950 Aureomycin® was successively used therapeutically. In 1949 McLean demonstrated that actinomyces bovis was inhibited by five gamma per ml of Chloromycetin® (13). Littman discovered that six strains of microorganisms were inhibited by concentrations above 103 gamma per ml and reported an apparent cure with Chloromycetin® therapy alone (19, 15).

Harvey, Cantrell and Fisher reported that penicillin is specific (4). They used 10 to 20,000,000 units intravenously followed by two to five million units intramuscularly for twelve to eighteen months. Recently penicillin V has been used orally in doses of five million units per day with apparent success. Penicillin therapy has resulted in cure rates in 88 per cent of the infected patients (4).

The subject of actinomycosis of the nervous system has recently been reviewed by Stevens who pointed out the frequently sudden onset and abrupt change in symptoms (16). This is supported by the present case in which symptoms appeared overnight and suggested a vascular accident rather than infection. Stevens also states that there is nothing about the abscess or meningitis of actinomycosis that distinguishes it from that caused by other organisms (16).

When actinomycosis bovis invades the central nervous system the infection is always secondary to a site elsewhere in the body. CNS infection may take the form of an abscess or meningitis. The spread may take place directly from an adjacent extracranial source such as the mastoid or paranasal sinuses or by or by metastasis from a distant source.

In the present case, the disease may have originated in the tonsils since there was evidence of chronic disease in these structures. There was also evidence of chronic, presumably healed, ear infection on the left suggesting the possibility of direct extension to the left cerebrum. However, this would seem least likely. Because of gastrointestinal symptoms and a mass in the right upper quadrant the abdominal source seems more likely as a primary site. The cerebral involvement then may have been secondary to one of the suggested primary sites or to the endocardial lesion.

SUMMARY

We have presented a case exhibiting a mass in the right upper quadrant, marked anemia, grade III systolic murmur of varying quality and a low

grade fever, followed by acute cerebral involvement presumably due to embolization. Actinomycosis bovis was cultured from the spinal fluid. Antibiotic therapy was dramatically effective and the patient remains well three years later.

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THE USE OF ANTIBIOTICS IN NONTUBERCULOUS INFECTIONS*

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INTRODUCTION

It is only 30 years since Fleming (1) reported the discovery of penicillin, and 17 years since Waksman (2) proposed the use of the term "antibiotics" to define chemical substances of microbial origin that possess antimicrobial activity. It is therefore understandable that ideas as to how they might best be used are just beginning to crystallize.

When first introduced, antibiotics were so effective in treating such a wide variety of diseases that there was a tendency to prescribe them freely, often without bothering to make a diagnosis. We also came to depend so heavily on these antibiotics that strict asepsis and good hospital hygiene were sometimes neglected. We now realize that antibiotics are not an unmixed blessing. The list of antibiotic induced diseases is a long one, and the problems of resistant bacteria are many. Fortunately, the days of "shot gun" therapy are over. The trend is now toward specificity; specificity in consideration of the infection, of the infected individual and of the antibiotic prescribed.

It is the purpose of this discussion to review some of the evidence of this trend, and to note some recent work which suggests that soon the use of antibiotics may be even more effective.

SPECIFIC INFECTIONS

It has become more difficult to generalize about the management of even a single syndrome such as pneumonia. As our knowledge of the etiologic agents increase, our approach to therapy changes.

Primary viral pneumonias, with the exception of psittacosis or ornithosis, are usually thought to be unresponsive to antibiotics. Now, there is some laboratory evidence that the primary atypical pneumonia virus of Eaton and Liu is also susceptible to a variety of antibiotics (3). This agent has been recovered from a number of patients who have had elevated cold agglutinin and streptococcus motters (4).

There is now a greater awareness of the many problems involved in the treatment of staphylococcal pneumonia. Not all strains of staphylococci react to antibiotics in the same way. Indeed, although it is now fashionable to consider all pathogenic staphylococci as resistant to penicillin, occasionally strains are still found that respond (5). Further, strains which, when growing rapidly, respond

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well to antibiotics, may be resistant within an abscess; not because of failure of the antibiotic to penetrate, but because within the abscess bacterial growth is very slow (6). The limitations of what might be considered optimal antibiotic therapy from *in vitro* studies are now more fully appreciated, and early surgical intervention, especially in the management of empyema and bronchiectasis, is employed.

The duration of antibiotic therapy in pneumonia also depends upon the etiology. Pneumococcal pneumonias are usually treated satisfactorily in a few days; staphylococcal pneumonias usually require four to six weeks of continued treatment.

In short, for ideal management of a patient it is necessary to know not only the virus or bacterium involved, but the response to antibiotics of the specific strain at a specific site. This means that good diagnostic bacteriology and virology laboratories are still an essential aid to treatment.

SPECIFIC INDIVIDUALS

There is an increasing awareness of the different responses of different age groups and individuals to the same antibiotics. It is becoming clear that premature and young infants cannot be treated by dosage schedules based on weight or surface area alone, as though they were small adults. The maturity of organs and enzyme systems involved in the pharmacology of the various antibiotics also must be considered (7). Thus premature and newborn infants attain and maintain very high blood levels of chloramphenicol even if the antibiotic is given just once every three days (8). Therefore overdosage is easy in these young babies. Unfortunately this has sometimes resulted in collapse and even death (9, 10). This syndrome should be recognized and differentiated from other causes of distress by all who treat young infants. After two or three days of chloramphenicol administration, there is abdominal distention, with or without vomiting then progressive pallor and cyanosis appear, and finally vasomotor collapse occurs. This is sometimes accompanied by irregular respiration. It has been suggested that the elevated and toxic blood levels result from the inability of these babies to conjugate chloramphenicol and from poor excretion of it. Proportionately much smaller doses must be given to them than to older children or adults. There is also evidence that excessively high blood levels may occur with kanamycin in young infants. These levels may cause permanent eighth nerve deafness and kidney damage (10). At the other end of the age scale, it has long been recognized that the aged are very prone to eighth nerve involvement after streptomycin.

There are of course individual variations in tolerance to antibiotics. Some individuals can take what would ordinarily be considered toxic amounts for prolonged periods without ill effect. A youngster with pyocyanus endocarditis was given 4 mgm per kilogram of body weight per day of polymyxin B for more than 100 days (for 10 days this was given intravenously) without apparent kidney damage (11). This procedure is not recommended except for desperate situations, and only when the therapy can be carefully controlled.

CHOICE OF SPECIFIC ANTIBIOTIC

The choice of a specific antibiotic depends upon knowledge of the specific etiologic agent, the antimicrobial spectrum of the available antibiotics, and the possibility of attaining good antimicrobial levels in the patient. This again presupposes good bacteriology. Since therapy must now often be started before the results of cultures are available, it also presupposes good epidemiologic and clinical knowledge to guide in the first choice of antibiotics. Indeed it is in starting treatment for the seriously ill patient, that there is rationale in using multiple antibiotics. Maximum doses of each are required, since the clinical effect is usually additive and only very rarely synergistic (12). This maximum dosage is frequently not achieved with ready-made mixtures, and they are not recommended.

The older established and better evaluated antibiotics should always be used first. Newer drugs and those with greater potential toxicity should be reserved for special cases. It is noteworthy that in many areas the great majority of staphylococcal strains are still sensitive to chloramphenicol, erythromycin and novobiocin (10). The ultimate choice will, of course, depend upon the response of the patient, and the results of testing for antibiotic sensitivity. However, there are limitations to the extent one may extrapolate from *in vitro* testing to the patient. This is especially true when the widely used disc method is employed, since not all antibiotics are equally diffusible in agar. Similarly the terms, "resistant" and "susceptible" are only relative. An antibiotic such as penicillin which may appear in the laboratory test to be ineffective, may be quite useful clinically since very large doses may be given safely. Indeed penicillin is often used with one of the other antibiotics as primary treatment in severe staphylococcal disease.

The choice of a particular antibiotic is often made difficult by the literal flood of new derivatives, each with a supposed virtue of achieving higher concentrations in the blood faster than previous products. Yet clinical effectiveness depends upon the antibacterial activity, not concentration of antibiotic in the blood. These do not necessarily go together, as was shown recently, for example, by Hirsch, Kunin and Finland (13) with erythromycin propionate and triacetyl oleandomycin. In light of the barrage of advertising literature, a recent editorial in *Pediatrics* is very timely. "We need carefully designed and controlled clinical trials—not testimonials to judge superiority. All too often this is lacking" (14).

OUTLOOK FOR THE FUTURE

The future holds great promise for even further specificity of antibiotic therapy. This may be illustrated by current investigative work in three fields.

First there is promise of more rapid etiologic diagnosis by the use of fluorescent dye techniques. Briefly, these methods use fluorescein tagged antibodies as an immunochemical stain for smears of clinical specimens. When the tagged antiserum is put in contact with homologous or specific antigen, precipitates form and fluorescein-antibody is fixed. The unreacted proteins are washed away. Examination of the smear under the fluorescence microscope then reveals the brilliant yellow green glow from the deposited fluorescent antibody, thus showing the presence and localization of the specific organism. A remarkable feature of

this technique is that positive identification of etiologic agents can be made even when they are present in very few numbers, among many contaminating agents and regardless of whether they are living or dead. The time required for diagnosis is cut to as little as one hour for some bacteria, and to no more than 24 hours for some of the viruses. This technique originally introduced by Coons as a research tool is now being applied to routine diagnosis. At the Communicable Disease Center of the Public Health Service more than 23 organisms pathogenic for man have already been identified with fluorescent antibody (15).

Secondly, we are beginning to learn more precisely how various antibiotics act on susceptible bacteria. This may well lead to new and more effective chemotherapeutic agents. Thus, it now appears from the work of Lederberg (16), and others (17, 18), based on both biochemical and morphological evidence that the primary action of penicillin is to interfere with the synthesis of the bacterial cell wall. A definite sequence of events apparently takes place. For example, Hahn and Ciak (18) demonstrated the lysis of *E. coli* by penicillin under the phase contrast microscope. They showed that the contents of the penicillin treated bacteria extrude as globular structures from the enclosing cell membranes. Then without the protection of these membranes against osmotic and mechanical forces, these globules disintegrate. The chemical reactions involved in the synthesis of bacterial cell membranes are therefore being investigated for clues to better antimicrobial therapy.

Finally, although all our antibiotics by definition were originally obtained from microbiological fermentations, there is now a good possibility that many may soon be synthesized commercially. The structural formulas are now known for the penicillins, streptomycins, tetracyclines, chloramphenicol and novobiocin (19); those of erythromycin and oleandomycin are under investigation (20). Chloramphenicol has been produced synthetically since 1949. In 1957, Sheehan and Henery-Logan (21) reported the chemical synthesis of penicillin V. More recently, Batchelor, Doyle, Nayler and Rolinson (22) isolated pure 6-amino penicillanic acid from penicillin fermentations carried out in the absence of added side chain precursors. Since the various penicillins may be regarded as acyl derivatives of this parent amine, and since this amine can now apparently be readily prepared, it must be considered as a most important chemical intermediary for the preparation of new penicillins. To quote from a recent comment in *Lancet*, "The consequences (of this work) could be far reaching . . . New approaches to the problems of resistant staphylococci should be feasible, and means may be found for enhancing the activity of penicillin type compounds . . ." (23). So-called "Tailor-made" antibiotics may soon be available.

In summary, the current practice and the future outlook for use of antibiotics is clearly toward greater preciseness in considering the infecting agent, the infected host and choice of antibiotic.

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AN ASSESSMENT OF ORAL ANTIDIABETIC THERAPY

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When tolbutamide became an established form of oral diabetic therapy, it had to measure up to insulin as a standard for therapeutic comparison. The generally satisfactory experience with tolbutamide now makes this drug the standard for comparison by which all other modifications of the original sulfonylurea formula and unrelated compounds must be measured. It will be the purpose of this presentation to answer two questions: do these modifications represent a contribution, and are they safe? In addition, an attempt will be made to describe variable responses to the same drug by the same patient.

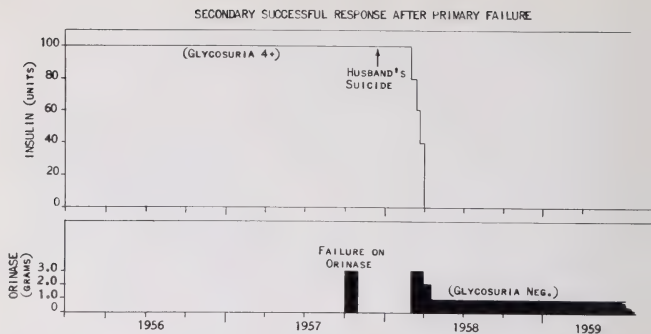
VARIABLE DRUG RESPONSES BY THE SAME PATIENT

As with insulin, diabetic patients exhibit altering and variable responses to the oral agents according to altering physical stress. Primary and secondary tolbutamide failures have been dogmatically dismissed as being insulin deficient in the physiological sense. That certain emotional and psychological factors in these patients may alter their responsiveness to these drugs is illustrated by the cases shown in figures 1 and 2.

Figure 1 demonstrates the primary failure of tolbutamide therapy in a 52 year old woman in whom the daily requirement for 100 units of insulin could not be influenced in the slightest by maximum amounts of tolbutamide while she was followed carefully in the hospital. Several weeks after the suicide of her husband when the patient eagerly sought a transfer to tolbutamide and overcame all medical resistance to her request, she was able to effect a successful change from her large insulin dose to one gram of tolbutamide, a dose which has been maintained for almost two years. No attempt has been made as yet to probe into the psychodynamics of this bizarre phenomenon.

Figure 2 illustrates a cyclical variation to responsiveness in a woman whose introduction to diabetes occurred during a severe agitated depression accompanied by ketosis. Following a period of insulin therapy an effective change to tolbutamide was accomplished. Then without explanation a steadily increasing dose of tolbutamide was required to the point of failure to control the diabetes and insulin had to be reinstituted. This physiological alteration accompanied a recurrent depression which responded to electro-shock therapy during which time insulin was continued. Parallel with her clinical improvement the insulin dose was reduced and tolbutamide reinstituted as daily therapy for another half year. Twice more this cycle was repeated, each time the first portent of the erupting emotional crises appeared in the failure of usual small doses of tolbutamide controlling the diabetes. By the second and third depressions the psychiatrists had instituted an alarm system whereby any increase of tolbutamide requirement would be reported to them as the sign of oncoming melancholia.

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PATIENT R. F.
FEMALE, 52 YRS.
D. M. 5 YRS. DURATION

FIG. 1.

MENTAL DEPRESSION
AND THE
CYCLICAL RESPONSE TO ORINASE



PATIENT S. W.
FEMALE, 62 YRS.
D. M. ONSET IN 1952
IN KETOSIS AND
SEVERE DEPRESSION

FIG. 2.

The first patient represents a primary failure and secondary success. The second patient was a primary success and secondary failure on a cyclical pattern. One wonders whether some of the other primary or secondary failures with oral diabetic therapy may be due to a basic emotional dependency upon insulin, injections, and the obvious associated implications of a masochistic need?

Variations by the same patient in response to different agents is illustrated in the case of a 26 year old man with hemophilia who was well controlled with 60 units of insulin daily. Unfortunately the patient presented a desperate emotional problem because each injection of insulin produced a huge hematoma. An attempt to achieve replacement of the insulin with tolbutamide failed. With some reluctance DBI was started and doses of 50 mgm a day effected a reduction and, finally, abolition of the need for insulin, with excellent control of glycosuria and normal blood sugar levels. Soon after he required 100 mgm of DBI, then 150 mgm, and finally 200 mgm which could not control glycosuria or ketonuria without severe nausea and diarrhea. A few days of insulin therapy were effective in obtaining control of the diabetes and a second trial with tolbutamide proved successful. Since then he has been managed with a half gram of tolbutamide daily.

Such dramatic instances make it evident that considerable fuzziness and overlapping will characterize any attempt to delineate sharply the areas of action and superiority for one drug over another.

EXPERIENCE WITH OTHER ORAL DRUGS IN DIABETIC THERAPY

A comparison can be made of three sulfonylurea compounds tolbutamide (Orinase[®], Upjohn), chlorpropamide (Diabenese[®], Pfizer), and metahexamide* (Melonex[®], Lilly; Euglycin[®], Upjohn). The actions and therapeutic range for all compounds are identical as illustrated in Figure 3. The only therapeutic differences lie in the relative increased potency of the newer compounds whose effective dosage is in the range of one tenth (metahexamide) to one third (chlorpropamide) that of tolbutamide. It can be seen that this increase in potency is associated with an increase in serious side effects and toxicity, especially in liver damage. There is no decrease in side effects despite the advertisements.

For the patients with "maturity onset" diabetes the generally accepted figure of 50 to 75 per cent successful applicability is equally true for each of the sulfonylurea compounds and their similar therapeutic spectrum is illustrated in Figure 4. It is apparent that only a fringe of a few per cent may reveal superior results from one of the new modifications. Limitations of juvenile diabetes, unstable diabetes, ketosis, etc, which have characterized the early experience of tolbutamide therapy hold true in identical fashion for chlorpropamide and metahexamide. Where the former fails the latter two drugs will not succeed so that the newer agents will not reduce the hard core of insulin deficient patients to any degree.

On the other hand, our experience with phenformin limits its usefulness to less than 20 per cent of the diabetic population which includes a number of mild

* Withdrawn from clinical trials now.

COMPARISON OF SIDE EFFECTS AND TOXICITY OF ALL ORAL AGENTS

DRUG	DOSAGE RANGE IN MG.	G.I. INTOLERANCE	LIVER DAMAGE	SEVERE HYPOGLYCEMIA	ACETONURIA	NEUROLOGIC EFFECTS
TOLBUTAMIDE	500 - 3000	0	0	0	0	0
CHLORPROPAMIDE	250 - 1000	+	+	+	0	+
METAHEXAMIDE	50 - 250	+	+	0	0	+
DBI (PHENFORMIN)	100 - 150	++++	0	0	+	0

FIG. 3.

PERCENTAGE OF ALL DIABETICS RESPONSIVE TO ORAL AGENTS

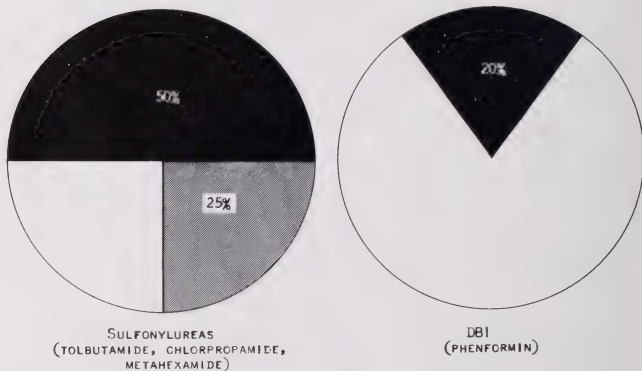


FIG. 4.

diabetic patients not requiring insulin in whom asymptomatic glycosuria can respond to therapeutic but minimal dosage of DBI. Limitations of therapeutic range will be described in the section devoted to side effects. We have not been able to duplicate the purported claim that DBI will abolish, reduce, or stabilize the insulin requirements in a single insulin-treated patient. The most encouraging results with DBI have accompanied its use as a supplement to existing tolbutamide therapy in some primary and most secondary failures. Totally depancrea-tized human beings on DBI require bi-weekly doses of insulin along with DBI. With this in mind, and recognizing the possible synergistic insulin-like effect of tolbutamide in such cases of DBI intolerance, it became apparent that it could

be generally useful to employ suboptimal doses of DBI, such as 50 mgm per day, with one to two grams per day of tolbutamide. This was first begun with secondary failures of tolbutamide therapy. Secondary failures have been presumed to represent some block by an adaptive mechanism to the action of this sulfonylurea. It has been possible in such instances to regain therapeutic success after a temporary period of insulin therapy, or by replacing the tolbutamide with another sulfonylurea derivative. However, with small doses of DBI, it was possible to overcome the failure of tolbutamide in about 150 patients who were then able to continue with total oral therapy without any side reactions from DBI. More recently we have employed the same technique in some primary failures with tolbutamide. These are adult patients in whom the 3 gram maximum dose of tolbutamide proved ineffective in controlling the glycosuria and hyperglycemia after three or four days. It was found that the addition of 50 mgm of DBI to the tolbutamide dose very often effectively restored satisfactory control. At this point the tolbutamide could be reduced, and then the DBI discontinued. Whenever the tolbutamide was discontinued in this combined therapeutic approach, glycosuria recurred.

Since all side reactions can be avoided, this technique of combination therapy offers the safest method of DBI administration in addition to providing a solution for tolbutamide resistance.

Of some 1000 diabetic patients attending the outpatient clinic of The Mount Sinai Hospital, about 200 are treated by mild dietary restriction alone, about 400 require insulin and the remaining 400 use the oral agents. In the latter group, 329 patients are well controlled by tolbutamide alone, 50 use a combination of tolbutamide with DBI, 19 receive chlorpropamide, and three are treated with metahexamide. The disproportionately small number of patients getting chlorpropamide and metahexamide represents the unwillingness of the clinic physicians to resort to these more toxic drugs in the face of satisfactory therapeutic success with tolbutamide in the bulk of patients. Furthermore, the contrast between the safety of tolbutamide therapy and the added complications of constant surveillance of hematologic and liver function studies necessary with chlorpropamide and metahexamide treatment made the former agent most desirable and economical for the patients and simplest for the physicians. In private practice, roughly the same distribution is noted with about one half the patients getting tolbutamide and the remainder using insulin. Combination therapy with either sulfonylurea compounds or DBI and insulin has proven useless not only as a therapeutic failure, but also because it causes anxiety in both patients and physicians.

SIDE EFFECTS AND TOXICITY

In May 1957 at a meeting of the Food and Drug Administration which was considering the public release of tolbutamide Dr. Perrin H. Long stated that his vast experience with thousands of analogues of sulfonamide would lead him to expect no toxic effects when the compound contained a methyl group in the para position of the benzene ring. This prediction has since been substantiated by the

insignificant number of side effects or toxic reactions due to tolbutamide therapy. More important than the frequency of occurrence should be the nature of the adverse and undesirable reactions associated with the drug. It is evident that conditions such as liver damage carry greater weight than skin rashes in analyzing comparative toxicologic data. Figure 3 illustrates the presence or absence of certain serious side effects and toxic reactions associated with each one of the oral agents.

Gastrointestinal tolerance for tolbutamide is so high that the therapeutic ceiling of 3 grams maximum can be exceeded many fold without distress. In striking contrast every one of the other three agents has a distinct maximal dose which often is associated with inability to be tolerated. In other words, 1 gram of chlorpropamide, 300 mgm of metahexamide, and 150 mgm of DBI produce nausea and pyrosis in 25 to 50 per cent of the patients in our series. DBI unfortunately is limited in obtaining full therapeutic effects because of the inherent tendency to effect the central nervous system center for nausea and vomiting in more than half of the patients whenever the therapeutic dose is reached. This untoward effect is even more undesirable since the commonly selected patients for DBI therapy usually include those juvenile and "brittle" diabetic patients most dependent upon insulin and most easily succumbing to diabetic ketosis. Anorexia, loss of weight, listlessness, and intermittent acetonuria without glycosuria are further indications of overdosage with DBI.

Both metahexamide and chlorpropamide, in the absence of the hypoglycemia, have produced bizarre neurologic phenomenon such as asthenia, ataxia and vertigo. It is the author's opinion that the purported advantage of more pro-

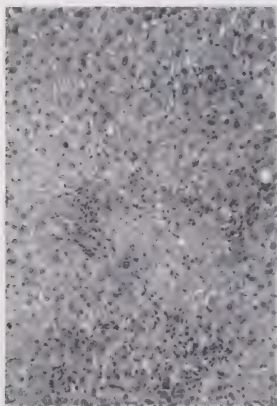


FIG. 5. (left) Liver biopsy from metahexamide jaundice revealing central lobular necrosis.

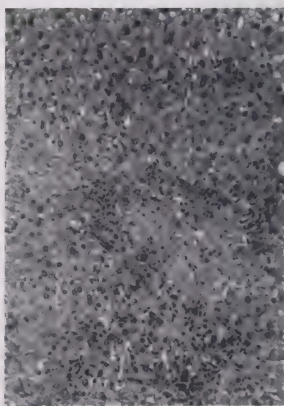


FIG. 6 (right). Liver biopsy from chlorpropamide jaundice showing biliary stasis.

longed hypoglycemic effects from chlorpropamide has been a disadvantage inasmuch as the elderly, senile, arteriosclerotic diabetic patient may suffer irreversible brain damage from such a "beneficial" effect.

Hepatic dysfunction and liver damage of appreciable or significant degree have not been reported so far in the 500,000 patients using tolbutamide in this country. On the other hand, a number of cases from the other sulfonylurea compounds have been observed. It has been learned that of 1800 patients using metahexamide, at least 10 cases of jaundice have been reported. The author has encountered three others. A 56 year old man with mild diabetes for ten years had been managed successfully with 1 gram of tolbutamide daily for one year. A clinical trial of metahexamide 300 mgm daily was carried out and on the 24th day, mild jaundice developed with chemical confirmation of obstructive icterus. Liver function studies were otherwise normal and a biopsy of the liver revealed central lobular necrosis with focal necrosis and mononuclear cell infiltration. This pathologic finding, illustrated in Figure 5, resembles the liver damage observed with sulfanilamide. In contrast to this type of liver damage we have observed two patients with jaundice due to chlorpropamide in whom the picture resembled that of cholestasis. Figure 6 represents a section from a liver biopsy of a 67 year old woman who had diabetes mellitus for 15 years and required about 100 units of insulin daily. Three weeks after she began receiving chlorpropamide 250 mgm daily, she developed obstructive jaundice which lasted almost three months. Liver biopsy revealed hyperergic cholangiolitis, severe cholestasis (biliary calculi) and focal liver cell injury suggestive of a drug reaction. (I am indebted for both slides and interpretations to Doctors Hans Popper and Fenton Schaffner.) From other reports, it is apparent that a significant number of patients with jaundice of the cholestatic type have been and will continue to develop from chlorpropamide therapy while jaundice due to central lobular necrosis will characterize this more serious toxic effect in patients receiving metahexamide. It seems that carbutamide was withdrawn for even less frequent toxicity.

As one glances at Figure 3 and compares the side effects and toxicity for the newer oral agents with the area of population covered by the therapeutic spectrum of Figure 4 it should become apparent that the maximum therapeutic effectiveness with maximum safety is to be found in tolbutamide. If serendipity be responsible for the entire field of oral agents in diabetic treatment, then the same happy accident has given us the most widely applicable and safest of these agents in the form of tolbutamide.

PERICARDITIS AND PLEURITIS IN ACUTE MYOCARDIAL INFARCTION

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Observations in recent years have indicated the need for a reevaluation of the place of pericarditis in acute myocardial infarction (1-9). From the early descriptions of this disease, fibrinous pericarditis was known anatomically to accompany acute coronary thrombosis with through and through infarction. Nevertheless, such pericarditis was considered of clinical significance only in that it produced a diagnostic, transitory rub. This appeared in 10 to 20 per cent of cases, usually on the second or third day. It was thought not to contribute to the symptomatology, clinical course, or prognosis of the attack, and required no therapy. On pathological examination, the incidence of fibrinous pericarditis in myocardial infarction has been variously reported between 15.5 and 80 per cent (10, 11); when present, it is localized over the infarct in about three fourths of cases, and is generalized in one fourth (11). Instances have been described in which the pericarditis was situated at a distance from the infarct (1).

Rarely has the combination of myocardial infarction and significant pericardial effusion been noted in pathological examination (12-14), and effusion of 50 cc or more is said to occur in 15 per cent of cases (11). Master and Jaffe described the first case of effusion diagnosed clinically (15) and several cases were reported sporadically in the ensuing years (16-18).

Following the introduction of anticoagulant therapy, the incidence of hemorrhagic pericarditis and hemopericardium has seemed to increase (19-23), often as a result of excessive medication, but also when the prothrombin time was not unduly prolonged. In the latter circumstance, anticoagulant drugs may have been an aggravating factor. In one case hemorrhagic pericarditis following myocardial infarction and anticoagulant therapy terminated in constrictive pericarditis (4). Although hemorrhagic pericarditis, pericardial effusion and hemopericardium doubtless occur more frequently than these relatively few reports suggest, their incidence would still appear to be quite low. The author has personally encountered five cases (including the fatal one which forms the basis of this report), an incidence of approximately one per cent. All had received anticoagulant drugs with prothrombin times well within therapeutic levels.

During the past four years, Dressler has observed 53 cases of myocardial infarction with pericardial and pleural effusion or pneumonitis (7). Transitory rales at the left base are common during the first few days of myocardial infarction but, in the past, pleural effusion and significant pulmonary changes were considered to occur only as a result of congestive failure or pulmonary

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infarction. Recently hemorrhagic pneumonia has been observed postmortem(24). Dressler has applied the term "post-myocardial infarction syndrome" to the cases he has observed and has pointed out their close similarity to benign, non-specific pericarditis and to the "post-commissurotomy syndrome." In his cases the course differed from that usually encountered in myocardial infarction in that after the first days the fever persisted; recurrent pleuro-pericardial pain appeared; when a pericardial rub was audible, it developed later than usual and persisted; signs of pericardial and pleural effusion and of pneumonitis were common. These findings usually occurred several weeks or months after the onset but sometimes appeared during the first week, and recurrent episodes were quite common for weeks, months or longer (25). Adrenocorticoid therapy was very effective. The pericardial effusion, which was frequently hemorrhagic, rarely required tapping. The prognosis was excellent, the one fatality being associated with excessive anticoagulant drug therapy.

Dressler has grossly estimated the incidence of the "post-infarction syndrome" at three to four per cent, which, we have noted, is considerably higher than that seen in our experience or in that of others. As a result, the existence of a specific pericardial syndrome in myocardial infarction remains an open question. Because of the diagnostic and therapeutic considerations, it is important to resolve this. The following case is significant since the diagnosis of pleuro-pericarditis made clinically was confirmed at necropsy. The patient had responded well to steroid therapy; death was very sudden and probably the result of ventricular fibrillation, unrelated to the pericarditis.

CASE REPORT

S. F., a man of 61, had undergone subtotal gastrectomy for duodenal ulcer six years previously. One year previously he suffered an acute myocardial infarction, with diaphrag-

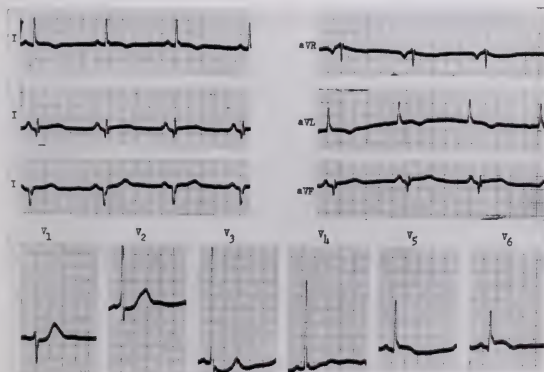


FIG. 1. Electrocardiogram taken 1/27/59 indicating lateral wall infarction.



FIG. 2. X-ray of chest showing enlargement of the heart.

matic infarction, following which he was asymptomatic except for occasional mild precordial pressure. He was on prolonged anticoagulant therapy but the dosage was probably inadequate. Three days prior to admission he began to experience recurrent substernal pain while at home.

Examination revealed occasional fine rales at the right base and bradycardia, pulse rate 50 min. There was no pericardial rub, the liver was not palpable, the blood pressure was 120/90, there was no edema. The temperature was 101°F., the serum glutamic transaminase was 169, sedimentation rate 37 mm., prothrombin time 15 sec. with a control of 13 seconds. The electrocardiogram showed previous diaphragmatic infarction (Q in 2, 3, AVF), and ST elevation in $V_{5,6}$ indicating lateral wall infarction. (Fig. 1). Two days later, the ST segment was isoelectric and the T wave was definitely inverted in 1, AVL and V_{4-6} . Several days later, a large Q appeared in V_5 .

On the second evening after admission, he complained of substernal pain and dyspnea, and tachycardia, numerous premature beats and rales at the left base. The temperature rose to 103°F. The next morning the pain was severe and a loud, very diffuse pericardial friction rub was present for one day. On the fourth day the temperature fell to 101°F. and the patient felt better. There were inconstant signs at the left base. By the eighth day,

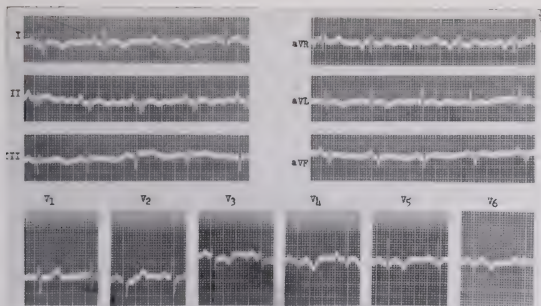


FIG. 3. Electrocardiogram taken 2/10/59.

the temperature was 99.4°F. and he felt well except for occasional mild pain in the region of the left shoulder. He continued well during the following week but on the twelfth day the temperature began to rise daily from 100 to 100.4°F. On the fifteenth day it reached 101°F. and on the next day 102°F. A small number of rales were present at both bases but there was no pericardial rub. Dicumarol[®] was discontinued and Meticorten,[®] 15 mg, q.i.d., was given. X-ray of the chest showed considerable enlargement of the heart to the right and left (Fig. 2). There were focal areas of atelectasis at both bases, and a small effusion on the right side. The electrocardiogram was unchanged from the one taken three days before (Fig. 3).

The next day (17th) the temperature was 99°F., and remained at that level or below. The signs in the lungs subsided and the Meticorten[®] was reduced to 10 mg. t.i.d. The patient felt very well when he was examined on the twenty second day, but two minutes later he died suddenly.

He received Dicumarol[®] from the second day in the hospital. On the fifth day the prothrombin time gradually rose from 15 sec. to 22 sec. and remained in the range of 18 to 20 sec. throughout, with a control of 12 to 13 sec. There was no evidence of bleeding from any mucous membrane or in the skin.

Postmortem examination revealed no cause for the sudden death. There was no evidence of myocardial rupture or pulmonary embolism. Diffuse hemorrhagic pericarditis was present in the stage of organization, most marked over the right atrial and posterior surfaces; there was 10 cc of pericardial fluid. The myocardium showed an area of acute necrosis in the anterolateral wall and evidence of previous infarction in the inferior wall. The coronary arteries were not occluded but each showed points of narrowing. In the lateral circumflex there was hemorrhage into a calcified plaque. The pleura was thickened and covered by hemorrhage and fibrin. There was no pulmonary infarction.

DISCUSSION

The clinical course and postmortem findings in this case confirm the fact that significant diffuse pericarditis, usually hemorrhagic, may occur as a complication of acute myocardial infarction and give rise to a rather typical clinical syndrome. Hemopericardium may develop in the absence of myocardial rupture. This type of pericarditis must be separated from the simple, benign, fibrinous pericarditis, usually localized, which occurs commonly in acute infarction and may produce a transitory rub two or three days after the onset, but causes no additional pain

or other symptoms or signs and does not influence the clinical course in any way.

In the case reported, the necropsy findings indicate that the hemorrhagic pericarditis appeared on the fourth day, with severe dyspnea and precordial pain aggravated by respiration, and caused fever and occasional chest pain during the next ten days. The recurrence of fever and pleural effusions after the twelfth day represented an acute hemorrhagic pleural reaction.

While it cannot be denied that the anticoagulant therapy given this patient may have aggravated the tendency to pericardial hemorrhage, it probably did not play a significant role in the hemorrhagic pericarditis, since the prothrombin time rose slowly and remained at or below 22 sec., and there was no evidence of bleeding elsewhere in the body. Nevertheless, the possibility of the occurrence of hemorrhagic pericarditis in myocardial infarction must be recognized as one more source of danger in using anticoagulant therapy in this condition. Indeed, it is rather surprising that hemorrhagic pericarditis does not occur more often, because the vascular granulation tissue in the pericardium during the process of organization, has a tendency to hemorrhage which is increased by the constant rubbing of the pericardial layers (1). In most cases this situation is not clinically significant and subsides quickly. However, as in idiopathic pericarditis, anticoagulant drugs may potentiate this condition. In the management of myocardial infarction, if a pericardial rub appears early and is evanescent, and there is no change in the patient's condition, the anticoagulant therapy should be continued. On the other hand, if significant pericarditis is suspected on the basis of additional chest pain or of a pericardial rub which is persistent or widespread, or appears later than the first few days, it would seem desirable to discontinue the use of anticoagulant drugs, and to observe the patient for signs of developing pericardial effusion.

The major differential diagnosis of pericarditis in myocardial infarction is from pulmonary infarction. It is very likely that the latter diagnosis, or that of recurrent or "extending" myocardial infarction, has in the past been made when, in fact, hemorrhagic pericarditis was present. As we have seen, the latter may be associated with pleural effusion or pulmonary signs. Evidence of pericarditis clinically and electrocardiographically should be sought when chest pain or fever recurs or persists following infarction. Usually the correct diagnosis is not difficult to establish but it must be remembered that a pericardial rub may be present in rare cases of pulmonary infarction in which the infarct is near the heart. It is of considerable practical importance to make the correct diagnosis since pulmonary infarction is an indication for continuation or initiation of anticoagulant therapy, whereas pericarditis demands the termination of such therapy, and the administration of corticosteroids if required. In mild cases the latter need not be given, in view of the possibility of rebound after discontinuation (23). Careful consideration of the character of the pain and the absence of new electrocardiographic changes or elevation of the serum glutamic oxalacetic transaminase should enable one quickly to exclude fresh myocardial infarction.

The necropsy findings in the case detailed above did not reveal the nature or cause of the hemorrhagic pleuro-pericarditis, which may be considered non-specific. In fact, in view of the low incidence of these complications in myocardial

infarction, the possibility exists that they are merely coincidental instances of non-specific benign pericarditis, not directly related to the infarction. This explanation appears untenable, except in rare instances, in light of the increasing number of cases that are being observed as knowledge of this complication of infarction spreads.

It is probable that the mechanism or etiology is multiple. When hemorrhagic pericarditis occurs within several days after the onset of infarction, it may merely represent a more severe degree of the benign fibrinous pericarditis which frequently accompanies infarction. This tendency to hemorrhage apparently is increased by the administration of anticoagulant drugs. When the pericarditis occurs after the first week, in the absence of anticoagulant therapy, and particularly when it recurs for weeks, months or even several years (6), Dressler's explanation of a sensitization reaction to necrotic cardiac tissue appears reasonable (7), as in cases of post-cardiotomy syndrome and benign idiopathic pericarditis. Indeed, this theory may also be applied to those cases in which the pericarditis occurs early in the attack. These may represent sensitization to a previous infarction or lesser myocardial damage. It has been suggested that hemorrhagic pericarditis is more apt to occur in myocardial infarction when ventricular aneurysm has resulted from previous infarction (9). In the case reported here, the hemorrhagic pericarditis, which began on the fourth day, may have been a direct mechanical result of the acute infarct or a sensitization to his previous infarct; the febrile, pleural reaction which occurred after the twelfth day may have been a sensitization reaction.

Whatever the cause of the pericarditis, corticosteroids are usually effective. In the case reported, there was prompt subsidence of fever and lung signs after administration of Meticorten®. This was almost certainly more than a non-specific effect of the drug.

Parenthetically, it may be pointed out that, in the case reported, both the acute and the old infarction had occurred without closure of a coronary artery. The recent infarction may have been related to the hemorrhage in the plaque in the left circumflex artery. Infarction without acute thrombosis is being reported with increasing frequency.

SUMMARY

There appears to be an increasing incidence of pericarditis, usually hemorrhagic, in myocardial infarction. This is independent of those cases resulting from anticoagulant therapy. Pleural and pneumonic involvement is often present and may predominate. A case is reported with non-specific postmortem findings.

Recognition of this complication is essential since anticoagulant therapy should be discontinued or avoided, whereas such treatment is indicated for pulmonary infarction or recurrent myocardial infarction.

Corticosteroids are usually effective in this pleuro-pericarditis but need not be used routinely, because of the possibility of rebound phenomena.

The course is usually benign, but, occasionally, tapping or pericardiectomy may be required. It is likely that pericarditis in myocardial infarction is of multiple etiology. One type, which is frequently recurrent, has been described

by Dressler as the "post-myocardial infarction" syndrome. It is similar to benign idiopathic pericarditis and postcardiotomy syndrome and may represent a hypersensitivity reaction to necrotic myocardial tissue.

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SOME IDIOPATHIC SYSTEMIC RESPONSES TO TOTAL BODY PERFUSION

I. THE POST-PERFUSION SYNDROME

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The repair of congenital and acquired cardiac lesions with the aid of extra-corporeal circulation has become a widely performed surgical technique. The performance of this type of surgery has carried with it a group of well-documented complications, including most particularly metabolic acidosis, atrio-ventricular conduction defects, and cardiac failure (1, 2). Following the use of extra-corporeal circulation, there are, however, a group of extra-cardiac systemic responses which appear unrelated to the primary surgical problem. We wish to present some illustrative case histories demonstrating the hematologic, gastrointestinal, renal and thermal responses to otherwise successful open heart surgery.

CASE REPORTS

Case #1

A sixteen year old girl was admitted to The Mount Sinai Hospital for surgical repair of an interatrial septal defect. On 11/11/58 she had an uncomplicated closure of this defect during which total body perfusion was carried out for a period of fifteen minutes. The pump oxygenator used was of the De Wall type (3).

Her immediate response to surgery was excellent. On the night of operation her hemoglobin was 13.6 grams per cent and white blood count was 7,000 cells per cu mm. Intercoastal drainage was minimal.

Serial daily hemoglobin and white blood count determinations revealed a progressive drop of hemoglobin to 9.6 grams per cent on the fourth postoperative day. The anemia was corrected, in part, by the transfusion of 500 cc of whole blood. Her hemoglobin levels then remained above 11 grams per cent for the next ten days. On her fifteenth postoperative day her hemoglobin concentration

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again fell to 10.6 grams per cent, and a second transfusion was given. During these two episodes of anemia, the serum bilirubin and plasma hemoglobin levels were not elevated.

The white blood count rose to 22,000 cells per cu mm on the third postoperative day and remained elevated above 20,000 per cu mm for seven days, when it gradually returned to normal. On the sixth postoperative day, atypical lymphocytes began to appear in the peripheral blood smear. These reached a maximum of 22 per cent on the tenth postoperative day and disappeared on the fourteenth day. Several heterophile antibody titres were not elevated during this period.

Although preoperative urinalyses were negative, the patient developed moderate albuminuria and microscopic hematuria one day after surgery. These findings persisted for two weeks and then disappeared. During this time, serial determinations of blood urea nitrogen did not rise above 20 mgm per cent, nor were there any urinary tract symptoms.

During the postoperative period, the patient's wounds healed primarily, and her chest x-ray was negative. However, she became febrile to 101°F on the night of surgery, and showed a subsequent daily rise of temperature to at least 100.5°F for 14 days. Throughout this period, there were no evident septic foci, and six blood cultures were negative.

The patient returned to a normal diet on her third postoperative day, and became ambulant on the fourth day. Throughout the period of anemia, fever, and leukocytosis, the patient looked well and had no complaints. She was active about the ward and was discharged on the eighteenth postoperative day. She has been seen in the Follow-up Clinic for eight months, during which time she has remained well.

Case #2

An eighteen year old girl was admitted to The Mount Sinai Hospital with a diagnosis of interatrial septal defect. On January 28, 1959, operative closure of this defect was performed with the use of extra-corporal circulation. Total perfusion time was 20 minutes. The defect was of the septum secundum type.

Her postoperative course was uneventful, except for the presence of anemia which reached 9.6 grams per cent on the twelfth postoperative day. This was corrected with a transfusion of 500 cc of whole blood.

Although there was no evidence of sepsis, the patient had fever to 102°F daily until the tenth postoperative day, and then daily to 100°F for six more days. Following this she remained afebrile.

The only other significant finding was 2+ albuminuria, and microscopic hematuria which began on the night of surgery, and persisted for seven days. At no time was there an associated rise in blood urea nitrogen.

The patient was discharged on her 25th postoperative day. She has remained well for eight months following surgery.

Case #3

An eleven year old boy had an uncomplicated surgical repair of a secundum type defect, using 16 minutes of cardiopulmonary bypass syphon. Immediately follow-

ing surgery, he developed severe oliguria which persisted for eight days and was associated with a rise in blood urea nitrogen to a maximum of 168 mgm per cent, and a rise in serum potassium to 8.8 mEq per liter. Following this, he developed an effective diuresis, and by the 17th postoperative day, his blood urea nitrogen and potassium had returned to normal levels.

Eighteen days after surgery, the patient developed gastrointestinal bleeding evidenced by guaiac positive stools and, at times, grossly tarry ones. He had repeated associated drops in hemoglobin levels to 9 grams per 100 cc. A total of 2,000 cc of whole blood were given over a five day period to return these levels to normal. The gastrointestinal bleeding abated spontaneously. Four weeks after surgery, a barium study of the upper gastrointestinal tract revealed a deformity in the duodenum strongly suggestive of duodenal ulcer.

The patient was discharged on the 42nd postoperative day. He has remained well for more than one year.

DISCUSSION

A review of the records of patients who have undergone surgical correction of intracardiac defects will make readily apparent the fact that certain complications can be expected to appear with considerable frequency. Where there is an increase in the number of closures of complex septal defects, the incidence of atrioventricular disassociation will rise. If the period of total cardiopulmonary bypass has been prolonged there will be increased difficulty in the management of acid-base balance.

The cases presented demonstrate a group of systemic responses to extracorporeal circulation which appear unrelated to the lesion which is treated, or to the duration of perfusion.

The hematologic changes seen after perfusion, are well demonstrated in Cases #1 and #2. At the completion of surgery, hemoglobin levels equalled preoperative levels; however, a significant drop of hemoglobin concentration was experienced by both patients between the third and fifth postoperative days, and again, during the second week following surgery. Blood loss alone cannot be considered an adequate explanation of this anemia. Intercostal drainage did not persist beyond forty-eight hours in either patient and during that time all overt loss was replaced on a volume-for-volume basis. The most likely explanation for the anemia is the premature breakdown of red blood cells because of the multiple blood donors used in priming the extracorporeal circuit, and because of the mechanical trauma to red blood cells during the perfusion. However, the failure of the serum bilirubin or plasma hemoglobin concentrations to rise above normal levels casts some doubt on this explanation.

The leukocytosis demonstrated by Cases #1 and #2 occurred precipitously within five days of surgery and returned to normal four days later. It is not explained on the basis of sepsis, since careful clinical search for a septic focus was negative in both cases. The appearance of atypical lymphocytes in the peripheral blood smear is unusual. Infectious mononucleosis could not be proven by subsequent elevation of heterophile antibody titres.

It may be postulated that the findings of albuminuria and microscopic hema-

turia displayed in Case 1 are due either to relative renal anoxia during the period of perfusion, or to air microemboli to the renal vasculature. Proof of this is lacking.

In the majority of patients undergoing open heart surgery, gastrointestinal activity is usually resumed within forty-eight hours. The presence of gastrointestinal ulceration and bleeding as a complication of cardiac surgery in young patients who were previously free of digestive symptoms has been described elsewhere (4). While no clear-cut etiology has been established, emphasis is placed on the role of stress and adrenocortical hyperactivity as the most likely causative agent.

A most significant, and clinically troublesome feature of all of the cases presented has been the presence of a low grade but persistent fever. The failure to demonstrate bacteremia by repeated blood cultures, the absence of any obvious septic foci, and the lack of a favorable response to antibiotics have suggested that infection is not the source of the fever.

Review of the postoperative courses of a group of patients who have undergone successful open heart surgery reveals the occurrence of a clinical syndrome which may best be termed the "post perfusion syndrome." It is characterized primarily by low grade fever in the absence of overt infection, recurrent anemia, leukocytosis, albuminuria, and microscopic hematuria. In one of the cases, gastrointestinal bleeding, and in another, the appearance of atypical lymphocytes in the peripheral blood smear were also noted. Many theories as to the etiology of this syndrome may be postulated. These include the effects of microemboli during perfusion, premature hemolysis of red blood cells because of the mechanical effect of extracorporeal circulation, and the presence of undetected septic foci. None of these theories lend themselves readily to proof. It is most significant that in all cases the syndrome was self-limiting and without apparent long-term residua.

In all cases management has been empiric. Anemia was treated with repeated transfusions. All overt blood loss through intercostal drainage tubes was replaced, volume-for-volume, with whole blood. Antibiotic therapy was maintained for two weeks following surgery, and then discontinued unless an overt source of infection persisted. The discontinuation of antibiotics has not provoked an exacerbation of symptoms or signs. A vigorous antacid regime was used as soon as the patient was able to resume oral alimentation. Fever was controlled with aspirin. At present, detailed clinical and experimental studies are in progress to elucidate the pathogenesis of this syndrome.

SUMMARY

A. Three cases are presented which illustrate the hematologic, gastrointestinal, renal, and thermal responses to patients undergoing successful open heart surgery.

B. Anemia, leukocytosis, hematuria, albuminuria, and fever are described as prominent clinical features of this "post-perfusion syndrome."

C. In a smaller group of patients, this syndrome includes gastrointestinal

bleeding, and the appearance of atypical lymphocytes in the peripheral blood smear.

D. The possible etiology of this syndrome is discussed.

E. A plan of management is described.

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RECOVERY FROM SUBDURAL HEMATOMA WITHOUT SURGERY

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The treatment of chronic subdural hematoma universally has been surgical (1). As soon as the condition was recognized, trephine openings were made and the hematoma drained. The only problem in these cases was to establish the diagnosis. The fairly typical syndrome was one of a patient with history of head trauma who, days or weeks later, manifested such symptoms as headache, drowsiness and alternating states of consciousness. The appearance of variable hemiparesis and oculomotor nerve dysfunction strengthened the suspicion of subdural hematoma and when the cerebrospinal fluid was xanthochromic the diagnosis was almost certain. In most of these cases a subdural hematoma was found and drained through the trephine openings in the skull (2).

What if the patient did not get worse or did not appear too ill? No surgical exploration was made. The patient's symptoms were attributed to cerebral contusion or edema caused by cranial trauma. In cases in which there was no history of head injury, the diagnosis was cerebral dysfunction due to causes other than trauma. Subdural hematoma was rarely suspected, particularly when the patient improved and remained well.

With the advent of angiography, the diagnosis of subdural collections of blood could be readily demonstrated. This procedure has been widely used in studies of all types of intracranial disease. In head injuries this method of investigation is almost routine in some clinics. In fact, there have been many instances in which unsuspected subdural hematoma was discovered by accident.

The typical angiographic finding of a subdural hematoma is the presence of an avascular space beneath the calvarium, extending two to four centimeters to the surface of the brain (Fig. 1). This is well seen in the arteriole phase. In the venous phase the large cerebral veins which always lie on the surface are pushed down away from the calvarium (Fig. 2). In unilateral subdural hematomas the anterior cerebral artery is often deviated from the midline to the opposite side. With such x-ray findings most neurologists and neurosurgeons have always agreed as to the presence of a subdural collection of blood and the need for immediate surgical intervention. When operation was performed in these cases, at The Mount Sinai Hospital, the neurosurgeons usually found a subdural collection of blood. This method of management of subdural clots has been standard in most clinics. What would happen if trephination or surgical drainage of clot were not carried out has rarely been questioned. Given a patient with a history of head injury who has fluctuating symptoms of cerebral dysfunction and in whom angiography reveals a subdural collection of fluid, (a) should immediate surgery be done and (b) if the course of such a patient is stationary or is getting better, what would occur if surgery were not performed?

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These questions have been raised during discussions concerning several patients with cerebral symptoms and x-ray findings of unilateral subdural collections of "hematoma". During the past two years the author has found that five such patients improved without surgery and subsequent angiography disclosed a disappearance of the unilateral subdural collection of fluid or hematoma. Presented below is the sixth case in which there was a bilateral subdural collection of fluid or hematoma.

CASE REPORT

Dr. P. L., who had been in active obstetric practice until the week prior to admission, entered the hospital with the chief complaint of difficulty in walking. Five weeks prior to admission the patient had tripped and fallen backwards, striking his occiput on a cement step. He sustained a laceration of the scalp which required six sutures. He was momentarily dazed but did not lose consciousness. For several hours he was somewhat "groggy" but then became rapidly well and remained so for two to three weeks, at which time the gait disturbance was first noted. The gait became abnormal. He walked with shuffling steps and had impulse to lurch forward. While driving a car there was a tendency to veer to the left. Concomitantly there was noted generalized slowing of activity and thinking. He was slow in dressing and had particular difficulty in buttoning his clothing. Some definite loss of recent memory was noted. His speech and voice became subdued.

On admission to the hospital Dr. P. L. was lethargic, listless, bradyphrenic and slow moving. He had difficulty performing simple calculation and showed some memory deficit. The face-hand test was strongly positive bilaterally, with frequent displacement to the left cheek of stimuli applied to the left hand and right face. The gait was shuffling and unsteady with veering to the left and, less often, to the right. The Romberg test was positive and he fell backwards. Tandem walking was poor. The finger-to-nose tests were performed with some tremor bilaterally. The heel-to-knee tests were slow and associated with dystaxia and tremor. The motor power was good throughout. The deep tendon reflexes were normal. There was a right Babinski and bilateral Chaddock signs. The sensory status was normal. There was infrequent blinking, decreased convergence, decreased optokinetic nystagmus in all directions and a central type of right facial paresis. The rest of the examination was normal.

The lumbar puncture revealed manifestly xanthochromic fluid under normal pressure of 130 mm of water. It contained a total protein of 68 mgm per cent and no cells. The electroencephalogram revealed bilateral cerebral dysfunction without evidence of a focal lesion. The x-rays of the skull were normal. Bilateral carotid arteriography revealed symmetrical subdural collections pushing the brain away from the inner table of the convexity at least 4 cms on the right and 3 cms on the left (Figs. 1 and 2).

The patient's neurologic status was carefully observed from four to six times each day throughout his hospital course. There was no change in the patient's condition for three days. Thereafter, there appeared a gradual improvement in

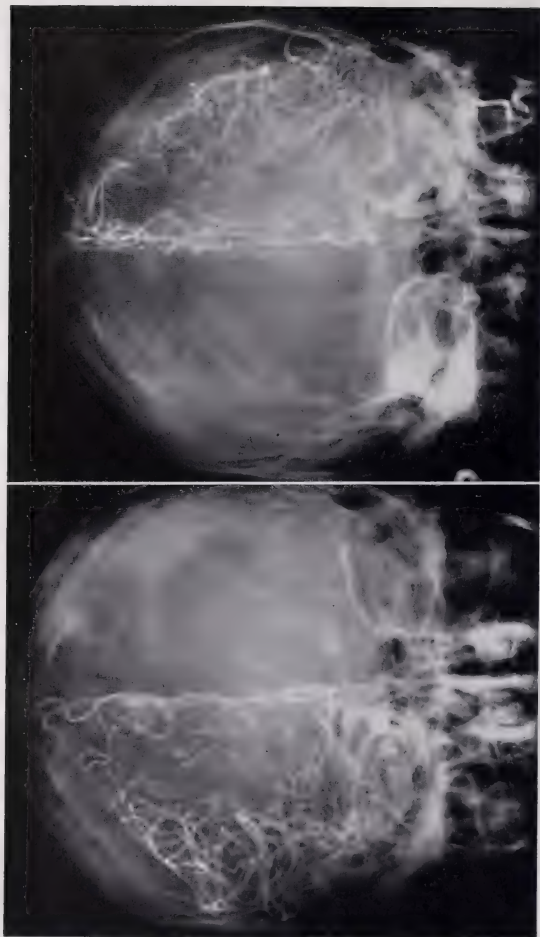


FIG. 1. A. Right angiogram. B. Left angiogram.

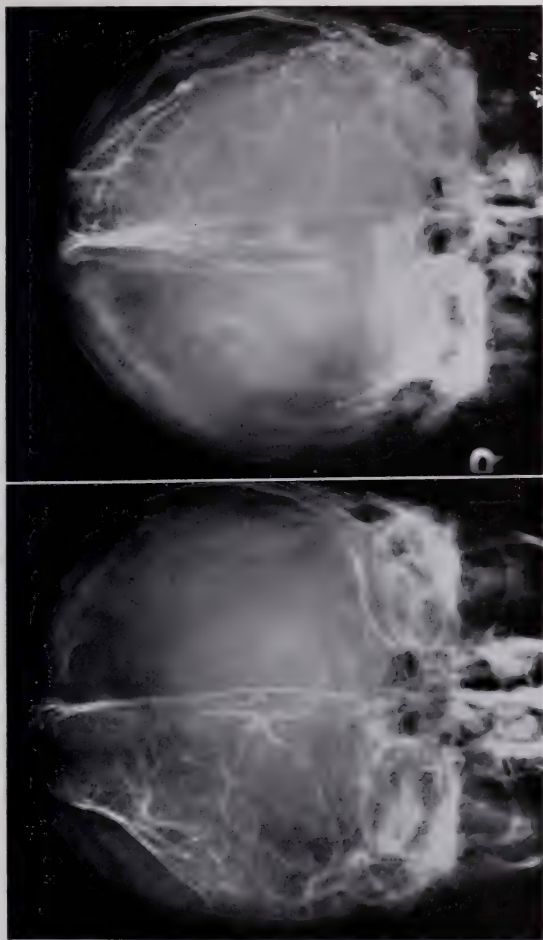


FIG. 2. A. Right angiogram. B. Left angiogram.

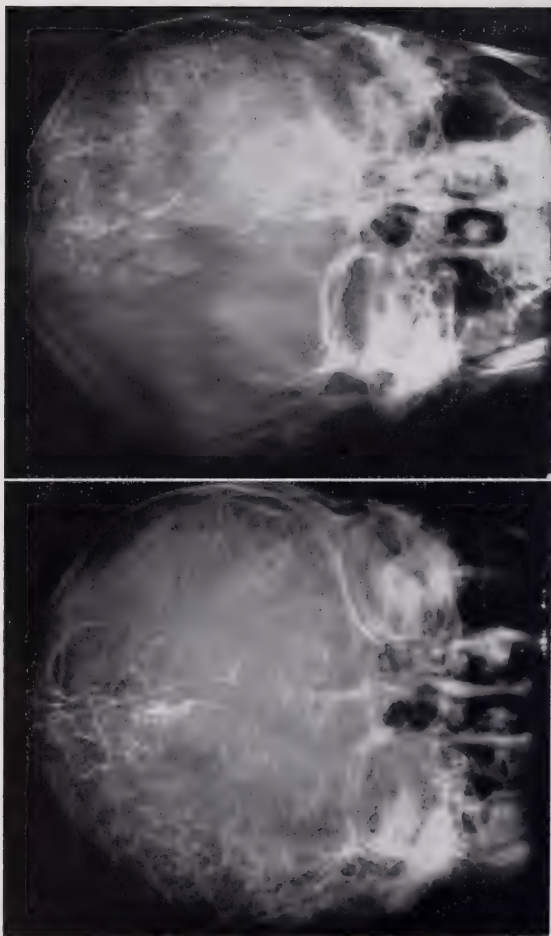


FIG. 3. A. Right angiogram indicating recovery. B. Left angiogram indicating recovery.

alertness, mental function and gait. Subsequently the pathologic reflexes disappeared. The Romberg became negative. The face-hand test became normal. The handwriting and optokinetic nystagmus also improved to become normal. Serial electroencephalography disclosed a lessening of the electrical abnormalities.

Twenty-eight days after the first arteriogram, repetition of bilateral carotid arteriograms disclosed marked improvement. The collection on the left disappeared, while that on the right was almost entirely gone (Fig. 3). It should be noted that by this time the patient had been asymptomatic for almost two weeks. The patient was discharged in good health and returned to his practice. He is still being examined periodically.

DISCUSSION

It is obvious that the subdural collection on the left was no longer manifest in the second angiogram (Fig. 3). On the right there was almost complete recovery. It should be pointed out that the interval between the two arteriograms was relatively short. If the interval were longer, it is probable that there would be complete resolution on both sides. This prediction is based on studies made by serial angiography over a period of months in five other patients with hematoma. As a rule the "hematoma" disappeared within a period of six to eight weeks. One of these cases has been followed for thirteen months without evidence of recurrence of the subdural collection.

As to the nature of the subdural avascular space seen in the angiograms, most neurologists, neurosurgeons, and roentgenologists agree that it represents a collection of fluid and in most instances it is blood; it might be in the form of fluid blood, clotted blood or a mixture of the two. Occasionally there may be a hydroma. In a series of 143 cases of subdural hematomas, Laudig, *et al.*, found two instances of hydroma (3). The type of subdural fluid present in the above and five other cases observed is not known. It has been suggested that a trephine and aspiration of fluid should be made for diagnosis, however, that has not been recommended because once a trephine is made, aspiration of the hematoma would be very compelling. Moreover, even if it were not aspirated, the fluid would tend to drain spontaneously through the needle opening in the burr hole so that improvement might be attributed to the drainage.

No matter what the nature of the collection, surgical intervention has been the rule in these cases in previous years. Now we find that the rule is not absolute. Patients can get better without surgery. The decision for surgery must depend on clinical judgment. The state of the patient's condition and the course of the illness should be the determining factors. If a patient becomes progressively drowsy over a prolonged period, evacuation of the clot is mandatory. The presence of a subdural collection of fluid by x-ray does not, by itself, indicate surgical intervention. The patient who is alert, has few symptoms or shows continuous improvement should be observed. Only if the course is downhill is operation necessary. However, it must be emphasized that there are no rules of procedure. Every case must be evaluated on an individual basis.

The fact that there was resolution in the case presented, suggests that some

patients with head injury who recover may have had unrecognized subdural hematoma. The exact incidence of such situations is as yet unknown. More information is needed but this cannot be obtained unless patients are permitted to recover without surgery.

SUMMARY

A patient with symptoms, signs, and laboratory, as well as angiographic evidence of bilateral subdural hematomas was observed over a period of six weeks. The patient recovered clinically without surgical intervention, as did five others who had unilateral subdural collections. The angiographic signs of subdural collection disappeared. These observations, which have been made since October 1958, suggest that there may be unrecognized instances of spontaneous recovery from subdural hematoma, particularly in cases in which this condition was not suspected or investigated by arteriography.

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Clinico-Pathological Conference

SUDDEN DEATH IN PATIENT WITH SUSPECTED MITRAL STENOSIS

Edited by

FENTON SCHAFFNER, M.D.

A 57 year old Danish upholsterer was admitted to The Mount Sinai Hospital for evaluation prior to mitral commissurotomy. He had been well until four years earlier when he developed vague episodes of daytime dyspnea. A year later, because of increasing dyspnea, he consulted his physician who found excessive "body water" although the patient was aware of no edema. The symptoms quickly responded to diuretic and digoxin therapy. Aside from occasional mild attacks of paroxysmal nocturnal dyspnea, he was well until eight months prior to admission when he developed progressive anorexia and dysphagia, especially with meat, which seemed to stick high in the chest and often was regurgitated. Hot flashes and sweating around the head and neck also developed. Irregular heart action was noted by his physician five weeks prior to admission.

The patient was studied during a series of short admissions to another hospital. Cardiac catheterization revealed the right ventricular pressure to be 65/8 mm Hg at rest and 91/24 mm Hg after exercise. The mean right atrial pressure was 7 mm Hg. The arterial oxygen saturation was 89% at rest and 91% after exercise. The P_{CO_2} , D_{CO} and hematocrit were 46 and 45 mm Hg, 6.9 and 8.3 liters, and 55% and 56% at rest and after exercise respectively. Oxygen consumption, respiratory quotient, blood flow and A-V difference were 232 and 430 cc/min., 0.76 and 0.96, 2.65 and 2.79 l/min., and 8.78 and 15.41 vol % respectively at rest and after exercise. Ventilatory studies at the same time showed a slightly reduced vital capacity and a marked expiratory delay. A dye dilution curve showed a single appearance of dye in 32 seconds with no evidence of intracardiac shunt. Electrocardiogram showed atrial fibrillation and right bundle branch block (Fig. 1). X-rays showed moderate cardiac enlargement, straightening of the left cardiac border and slight posterior displacement of the esophagus (Fig. 2). No systolic murmur was heard but M_1 was accentuated, and, early in diastole, a short murmur was found. Because of some disagreement as to the interpretation of the findings, the patient was referred to The Mount Sinai Hospital for further evaluation.

As a child the patient had a left otitis media with drainage which left him with impaired hearing in the left ear. No history of rheumatic fever was obtained. His appendix was removed at the age of 48.

On examination the patient did not appear to be ill. His pulse was 52/min. irregular and with some dropped beats. Blood pressure was 110/75 mm Hg and he was febrile. There was slight icterus. Evidence of old bilateral otitis media was found. The teeth were in poor repair. Some neck vein distension was present

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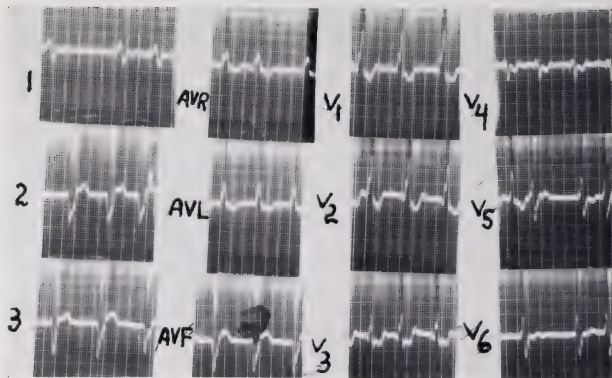


FIG. 1. Electrocardiogram showing atrial fibrillation and right bundle branch block.

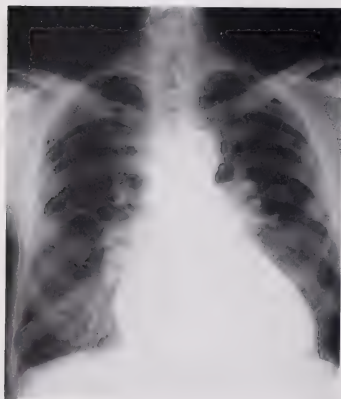


FIG. 2. Chest x-ray with generalized enlargement of the heart and increased hilar markings.

at 90°. The AP diameter of the chest was increased and the lungs were hyperresonant but no rales were heard. The heart was enlarged to the left. The rhythm was irregularly irregular and an apical diastolic rumble was heard. M_1 was accentuated. The liver edge was at the level of the umbilicus. The liver was firm, smooth and non-tender. Mild pretibial edema was present. The nailbeds and face were cyanotic when the patient was lying down. No other abnormalities were noted.

Red cells, white cells, granular casts, 2 plus albumin and 1.020 specific gravity

characterized the urine. Hemoglobin was 16 Gm% and hematocrit was 54%. White blood count was 12,800/cu mm with a normal differential. Sedimentation rate was normal as were the values of blood urea nitrogen, glucose, electrolytes, proteins, cholesterol, prothrombin time and phosphorus. The serum bilirubin was 1.7 mg% and the uric acid 10.5 mg%. Serology was negative. Venous pressure was 195 mm and the circulation time with Decholin* was 65 seconds. Stool guaiac tests were negative. The radioiodine uptake in 24 hours was 33%. Chest x-ray showed the heart to be enlarged to the right and left. The right atrial contour was elongated and prominent. Indentation of the barium-filled esophagus and obliteration of the retrosternal space were noted. The cardiac silhouette was prominent toward the left and posteriorly but the point of opposite pulsations was not elevated. The pulmonary vasculature was prominent and many Kerley lines were seen in both lower lung fields. Gastrointestinal series showed only antral spasm. Electrocardiogram showed atrial fibrillation, ventricular premature contractions and a right bundle branch block.

The patient was given a low sodium diet, mercurial diuretics, sedation and supplemental potassium. After four days the patient complained of difficulty in breathing and 0.25 mg of digoxin was given twice daily. The BUN had risen to 33 mg % and the bilirubin to 2.7 mg %. By the sixth hospital day, the patient had gained four pounds and appeared worse. A phlebotomy was performed which gave some relief. By the eighth hospital day, the patient again became dyspneic and the liver was felt to pulsate. The BUN was up to 52 mg %, CO_2 29.0 mEq l, chlorides 80 mEq l, sodium 121 mEq l and potassium 3.1 mEq l. Serum uric acid was 12.5 mg % and glutamic oxalacetic transaminase was 244 units. Another phlebotomy was done.

Because of disagreement as to the auscultatory findings, phonocardiography was done twice. The first sound was widely split as was the second sound. The first component of the first sound was diminished in intensity. A faint systolic murmur was present and an additional sound was heard in diastole, too late for an opening snap but early for a gallop. No diastolic murmur was recorded. Pulmonary function studies are shown in Table I.

On the 11th hospital day, the patient's heart returned to normal sinus rhythm. Edema was worse but the lungs were clear on auscultation and fluoroscopy. ECG was unchanged except for rather normal P waves and a PR interval of 0.20 seconds. Late that day while on the bedpan the patient collapsed and became apneic and pulseless. Emergency measures were of no avail and a terminal ECG showed chaotic heart action with a rate of about 30 which quickly proceeded to asystole.

*Dr. Charles K. Friedberg**: The case for today is an interesting one because in all analyses of cases presented at a clinico-pathologic conference, two problems are present: one is the raw material provided, and the other is the interpretation of the raw material. If the raw material is in any way inaccurate, then, of course, one is at the mercy of the data.

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TABLE I
Report of Pulmonary Function Studies

	Predicted	Observed	
		Supine	Standing
Lung volumes in cc			
Expiratory reserve volume.....		1280	
Inspiratory capacity.....		2490	
Vital capacity.....	3900	3760	4140
Residual volume (RV).....	1400	2170	
Total capacity (TC).....	5300	5930	
RV/TC.....	35%	36.6%	
Ventilatory function			
Maximum breathing capacity (L/min.).....	98	67	80

Intrapulmonary mixing (residual N₂ after 7 min. O₂ breathing)

Normal: 2.5% Observed: 3.13%

Arterial blood study		Normal	Resting	After exercise
CO ₂ content	vol. %	48-52	35.3	
O ₂ content	vol. %	19.0	18.9	18.9
O ₂ capacity	vol. %	20.0	19.7	20.0
O ₂ saturation	%	95-97	97	96
CO ₂ content (serum)	vol. %	55-60	43	
pCO ₂ (serum)	mm. Hg.	38-41	29	
pH		7.37-7.42	7.43	

No trapping of air on spirogram.

This case has a great deal that is not consistent. We have here a straightforward story of a man who presumably started with symptoms of left-heart failure, was treated for it, and did well. One can ask at this point if we are sure that the dyspnea was due to left-heart failure or to pulmonary or other causes, but I would say that the weight of evidence suggests left-heart failure. He had occasional attacks of paroxysmal nocturnal dyspnea, which also would not fit a pulmonary story. He developed progressive anorexia and dysphagia. A number of cardiac conditions are associated with dysphagia, notably aneurysms of the aorta, vascular rings and mitral stenosis with large pulmonary arteries. On the other hand, we do not know whether this patient had other causes for indigestion, so I am not inclined to make too much of this part of the story.

He had some admissions to another hospital and we are given data obtained there regarding a series of tests. This is what I mean about the dependence on the raw material, because the number of tests that were done is very impressive and the kind of tests done are those that would make one think they were done by clinical investigators, and therefore quite reliable. Analyzing them, we find first that cardiac catheterization showed very high pressures in the right ventricle

with a rise on exercise. Normal pressures do not rise on exercise in the normal individual. The mean right atrial pressure was slightly elevated. If we could trust this, we have an abnormality that requires explanation. It makes one wonder whether or not the dyspnea at the onset of the illness was indeed of cardiac origin or whether it was of pulmonary origin. The reason I am casting doubt on these data is that later, in this hospital, the arterial oxygen saturation was perfectly normal, so that we would have to assume that either the patient miraculously improved or some of the data were inaccurate. The CO_2 tension in the arterial blood, the diffusing capacity for carbon monoxide, all given with rest and at exercise, are rather formidable determinations, and one would think that people who undertake such examinations would do them very accurately. These reports indicate that the tension of CO_2 was greatly elevated, as one might expect with obstructive emphysema. The diffusing capacity is diminished. The hematocrit is 55 per cent, and if we accept the oxygen unsaturation of the arterial blood, we would conclude that this patient had a mild degree of polycythemia, secondary to arterial hypoxemia. Oxygen consumption, respiratory quotient, blood flow and A-V difference were determined. The cardiac output was greatly diminished and did not substantially rise with exercise. The respiratory quotient increased with exercise presumably because of hyperventilation. Ventilatory studies showed a slightly reduced vital capacity, and a marked expiratory delay. The slightly reduced vital capacity and the marked expiratory delay both are characteristic findings in patients with obstructive emphysema, so that again it looks as if, on the basis of the interpretation of these data, we have a patient who has obstructive emphysema and carbon dioxide retention, with pulmonary insufficiency as indicated by low arterial oxygen saturation. Dye appeared in 32 sec. This denotes a prolonged circulation time, i.e. congestive heart failure, but there was no evidence of an intracardiac shunt.

Other findings besides the dye studies tended to exclude the possibility of congenital heart disease as the basis for this clinical picture. The electrocardiogram showed atrial fibrillation and a right bundle branch block. No systolic murmur was heard. M_1 was accentuated, and early in diastole a short murmur was found, so that we have auscultatory findings compatible with mitral stenosis, but the protocol says because of disagreement as to the interpretation of the findings, the patient was referred for further evaluation.

This raises some question. Wholly aside from the fact that we are dealing with a case that is presented for clinical pathological conference, and one should always be a little suspicious certainly about being presented with a straightforward case of mitral stenosis studied for commissurotomy, we have here, first, a statement of findings which seem fairly unequivocal, findings of mitral stenosis but also fairly unequivocal findings of obstructive emphysema. There is no history of rheumatic fever, for whatever that is worth. I do not think we can use that too strongly, either to support or negate a diagnosis of mitral stenosis. Nothing in the clinical history or the description of the findings in this hospital, other than the comments about the hyperresonant lungs, indicates either that the breath sounds or other findings were suggestive of bronchopulmonary disease, such as

one might anticipate if we accept these pulmonary function studies as being accurate. We might have expected some comments about the nature of expiration or the presence of wheezing. On the other hand, on the basis of the signs in the heart, we really have no reason to question the diagnosis of mitral stenosis.

The liver edge was down to the umbilicus and mild pretibial edema was present. All these findings would be indicative of mitral stenosis with predominant right-sided heart failure. It is remarkable that we already have mention of such definite evidence of right-heart failure; and in addition to which the patient was slightly icteric, which I interpret as being due to severe degree of congestion of the liver.

It is surprising that we do not hear more about the left side of the heart and the changes in the lungs in view of the fact that this patient already has right-heart failure. The arterial oxygen saturation in this hospital was 97 per cent, so if there is any degree of polycythemia, we would have to attribute that to a primary, not a secondary polycythemia. I am inclined to dismiss that as not being adequate to justify such a diagnosis. The white blood count was 12,800 cu mm. Sedimentation rate was normal as were most of the blood chemistries, except the serum bilirubin which was 1.7 mg per cent, fitting the mild icterus, and uric acid was 10.5 mg per cent. I see nothing in the story or the findings to explain this elevated serum uric acid. There have been reports in polycythemia of gout with elevated serum uric acid. Many of those reports have been questioned. Uric acid could be elevated with marked degree of renal insufficiency but I do not see evidence of it at this point.

Venous pressure was 195 mm, which is elevated, and circulation time with Decholin* was 65 seconds. It is really too long for a good end point but we can at least say it probably indicates that there was heart failure.

I would just comment about the normal radio-iodine uptake because of the fact that there was some story about the patient sweating and having flushes. One might have considered the possibility of hyperthyroidism. Also, whenever atrial fibrillation is present and there is any doubt of the etiology, the question of masked hyperthyroidism is to be considered, but this diagnosis tends to be excluded by the radio-iodine findings. Dr. Brahms will discuss the x-ray films.

Dr. Sigmund A. Brahms†: On a gastrointestinal series there was no intrinsic abnormality in the esophagus to account for any dysphagia. There was also no evidence of an aneurysm of the aortic arch and no evidence of a vascular anomaly at the level of the arch. Barium traversed the esophagus without delay. The stomach showed no intrinsic abnormality; the distal part of the stomach and the antrum were not fully distended. Some increase in irritability in the antrum was noticed but the folds appeared intact with some thickening. The duodenal loop showed no abnormality intrinsically or extrinsically. I believe the evidence does not justify the x-ray diagnosis of a retrogastric mass or of an intrinsic abnormality in the stomach or in the duodenum.

On the chest film, the heart showed some enlargement of all the chambers. A slight impression was made on the barium-outlined esophagus at the level of the left atrium. We see this in generalized enlargement of the chambers of the heart.

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I did not think there was any disproportionate enlargement of the left atrium. There was a little calcification in the wall of the aortic arch. The aortic arch was not markedly elongated, and the pulmonary vasculature was tortuous. There was some increase in the prominence of the vessels in the hila, perhaps their first branches. I had the impression that the peripheral vessels were small. The features suggest pulmonary hypertension.

Dr. Friedberg: Did you see any evidence on the film of a double density?

Dr. Brahms: Yes, but the left atrium is no larger than the enlargement of the other chambers.

Dr. Friedberg: There was no distinct enlargement of the atrial appendage. Because of disagreement as to the auscultatory findings, phonocardiography was done twice. The first sound was widely split as was the second sound. The first component of the first sound was diminished in intensity. A faint systolic murmur was present and an additional sound was heard in diastole, too late for an opening snap but early for a gallop. This is quite a fine point since the opening snap might be regarded as occurring about .06 to .12 seconds after the second sound, and the gallop, if it is the gallop of a third sound, might be 0.05 to 0.08 seconds beyond that. No diastolic murmur was recorded. His electrocardiogram was unchanged except for rather normal P waves and a PR interval of 0.20 seconds. Later that day, while on the bedpan, the patient collapsed. He became apneic and pulseless. Emergency measures were of no avail, and terminal electrocardiogram showed chaotic heart action with a rate of 30, which quickly proceeded to asystole.

Let us start with a discussion of the differential diagnosis since we have the pulmonary function studies and since I pointed out before that the studies reported in another hospital were rather characteristic of those of decompensated obstructive emphysema, plus some impairment of pulmonary diffusion, which can occur with obstructive emphysema, if there is a great enough reduction in the pulmonary bed. In this hospital, there was no evidence of pulmonary insufficiency, that is, the arterial oxygen saturation was normal. As a matter of fact, most of the pulmonary findings were essentially normal. The residual volume was 36 per cent of the total capacity as compared to a normal value of less than 35 per cent. But some authorities require that it be more than 40 per cent to be abnormal, as in obstructive emphysema. At any rate, certainly this was not striking. The maximum breathing capacity was only slightly diminished and this too does not fit a case of obstructive emphysema of the kind that we would have to postulate if we were going to attribute this patient's right-heart failure to obstructive emphysema. No trapping of air was observed on the spirogram, another bit of evidence against obstructive emphysema.

The intrapulmonary mixing was likewise borderline. It is true that after breathing oxygen for seven minutes, the nitrogen concentration was 3.1 per cent whereas normally it is less than 2.5 per cent. This is certainly not in the range usually observed with severe obstructive emphysema. We have here a patient who neither presented a story of bronchopulmonary disease nor had physical signs of bronchopulmonary disease and whose pulmonary function tests were essentially normal.

I think there were also some values that we brushed over showing that the tension of CO_2 , normally 38 to 41 mm Hg, was 29 mm Hg. Instead of there being a retention of CO_2 , as reported on previous examination, there is actually a reduction of CO_2 . This reduction of CO_2 is, of course, compatible with congestive heart failure in which there is generally some degree of hyperventilation.

Of the intrinsic forms of pulmonary disease, we would ordinarily associate such a finding with pulmonary fibrosis, as in the condition termed the alveolar capillary block syndrome. But that is not compatible on the basis of the pulmonary function studies which showed that the vital capacity was virtually normal. In other words, if the pCO_2 was reduced because of pulmonary fibrosis with alveolar capillary block or impaired diffusion, one would have a rather nondistensible lung with a marked reduction in vital capacity. On the basis of these findings we can exclude pulmonary disease as the basis for this patient's heart failure.

On reading this history the other day, I called Dr. Popper and asked him whether I could see the electrocardiogram. I will tell you why I did that. You will recall that there was a statement of disagreement as to interpretation of findings in his previous hospitalizations. There seems to have been some disagreement here too. There is statement of a diastolic rumble and then there is a statement that there was disagreement of the auscultatory findings. Actually, if there was no doubt about the auscultatory findings, I would have no reason really to question the diagnosis of mitral stenosis. But the findings in the phonocardiogram do not support this diagnosis. The first sound which was previously described as being sharp on auscultation and compatible with mitral stenosis is not here described as being sharp; the first component of the first sound, which is due to closure of the mitral leaflets, was described as being diminished in intensity. No diastolic murmur was distinguished but there was a question of whether there was a sound somewhere between the time of the opening snap and the gallop. Usually when there is this much of a quibble about such phonocardiographic and auscultatory findings, we are dealing with a gallop sound or a gallop rhythm. When both the first and second sounds are split, it is not uncommon for a presystolic murmur to be simulated. My interpretation would be that the splitting of the first sound may well have been due to the right bundle branch block and that the other extra sound was indicative of a gallop rhythm. The electrocardiogram showed widening of the QRS complexes to 0.14 seconds with a tall notched R in V_1 indicating a right bundle branch block. In V_2 and V_3 a Q wave was present. The QS wave in leads 2, 3 and aVF may be part of the bundle branch block pattern in a horizontal heart but could also represent an old diaphragmatic infarction. Although in left bundle branch block it is usually difficult or impossible to recognize the occurrence of previous myocardial infarction, in right bundle branch block the presence of Q waves in these precordial leads is usually indicative of such a condition, that is, of an anteroseptal infarction. I am not at all inclined to accept the proposed diagnosis of mitral stenosis in this patient because of the equivocal story of the findings on auscultation, because the diastolic rumble that was described in one part of the protocol is not sup-

ported by two phonocardiographic studies and because the history in general would be an unusual one for mitral stenosis, though not impossible; namely, a man 57 years of age without any previous history developing gradual left-heart failure and then very rapidly in five weeks developing marked congestive heart failure of the right side with very little evidence of left-heart failure.

One might say that this patient could have had an intermittent diastolic murmur and that this suggests a tumor, but we do not have a story of syncope with change of position.

In this case we have the story of a patient who begins to develop left-heart failure and then goes rapidly into right-heart failure. His electrocardiogram showed a right bundle branch block, which could occur in a normal individual, in a patient with right ventricular hypertrophy of any cause including mitral stenosis but which also is common in patients with coronary disease and old myocardial infarction. Because of the right precordial Q waves, I would be inclined to think that this patient had an old anteroseptal myocardial infarction.

In addition, he may very well have had involvement of the right coronary artery, to account for an old diaphragmatic infarct. If we consider some of the explanations of bundle branch block, including some of the findings that have been made on postmortem examination of the septum by serial histological studies, then the prolonged PR interval becomes significant because some observers think that this plus the right bundle branch block pattern suggests an extensive septal infarction with partial bilateral bundle branch block.

I should say something about Bernheim's syndrome because we are dealing here with a man who did develop rather rapid and disproportionate right-heart failure. You remember the pulsating liver, the icterus, the edema, and the minimal findings in the lungs. Some patients with acute myocardial infarction develop right-heart failure with little or no preliminary left-heart failure. In those cases we have usually seen a septal infarct with an aneurysmal bulging to the right. The thought has been that this produces a functional pulmonary stenosis. I have some doubts about this interpretation in this case because the essence of the Bernheim syndrome is that the protrusion of the septum produces functional pulmonary stenosis in the absence of left-heart failure. While the right-heart failure was disproportionate here, I cannot say that there was no left-heart failure since the prolonged circulation time and the history suggests that the patient had left-heart failure initially.

In conclusion, I have suggested an old anteroseptal and probably a diaphragmatic infarct, with bilateral bundle branch block, possible aneurysm of the septum, with Bernheim's syndrome, and sudden death, most likely due to ventricular fibrillation.

Dr. Hans Popper†: Before going to the chest organs, in which obviously the main pathology was located, I want to quickly review the other organs to give

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us a background for the evaluation of the changes in the chest. The brain appeared rather edematous. In the posterior part of the temporal lobe area, we saw a small focus of encephalomalacia. This was confirmed by microscopic examination in which we found extensive arteriosclerotic changes. The thyroid showed evidence of involution rather than of stimulation. Hyperthyroidism could not have been part of the clinical picture.

The liver appeared enlarged. It weighed about 1700 grams. On the cut surface we saw the classical picture of prolonged subacute hepatic congestion. In the centrilobular zone all liver cells had disappeared and only blood was found with the collapsed framework which was still present. In a few areas where the liver cells of centrilobular zone appeared well-preserved, severe bile stasis was noted, reflecting the slight jaundice with conjugated bilirubin usually present in chronic passive congestion of the liver.

The spleen was slightly enlarged, weighing 190 grams. The consistency was rubbery and the organ was markedly congested. Arteriosclerosis was present in the vessels of the spleen. It is always found earlier in the spleen and is rather prominent under these circumstances.

The adrenal showed severe congestion which may have had something to do with the electrolyte balance which was present. The kidneys showed passive congestion. They were of normal size and the cut surface revealed anemia infarcts and marked passive congestion throughout. Severe arteriosclerosis had developed in the larger as well as smaller vessels, but without involvement of the smaller arterioles. In skeletal muscle also the smallest arterioles were perfectly normal, with no evidence of either sclerosis or contraction.

The esophagus was normal and the history of dysphagia was not related to an intrinsic disease of the esophagus. There was a healing peptic ulcer in the first portion of the duodenum, probably explaining the radiologic findings in the duodenal bulb.

No fluid or adhesions were found in the pleural cavities. A slight degree of emphysema was present in the lungs. Some of the alveolar spaces appeared somewhat enlarged and on close inspection arteriosclerosis was noted in the pulmonary artery branches, more in the larger ones. Microscopically, this was intimal thickening with the medial layer not altered by fatty deposition; the characteristic picture of arteriosclerosis of the pulmonary artery usually reflecting increased pressure in the pulmonary system. In the lung parenchyma, the vascular tree was more prominent than normal but the most impressive picture was the tremendous amount of blood found in virtually every vessel. Pulmonary congestion was extensive in the absence of any pulmonary edema. Many heart failure cells had accumulated and the alveolar septa were thickened by fiber formation but there was no excessive fibrosis of any other nature. Severe passive congestion was the leading anatomical feature in this lung associated with vascular changes. We found some contraction of the arterioles. Spasm was present which extended also to the larger vessels. We saw rather impressive tortuosity of the pulmonary artery branches which were crowded with blood

and probably distinctly contracted. There was some increase in the musculature as well as an attempt of contraction judging from the arrangement of the nuclei. This never can be interpreted well in a postmortem specimen. The intima thickening was mild and did not produce any severe degree of obstruction to the pulmonary flow. The marked filling of the pulmonary capillaries would not have been as conspicuous if the pulmonary arterioles would have been more effective in preventing the blood flow into the capillaries. The contraction and thickening of the vessel walls, which I consider secondary to an increased pulmonary pressure rather than primary, also involved the larger elastic pulmonary artery



FIG. 3. Pericardium showing violin-string adhesions.

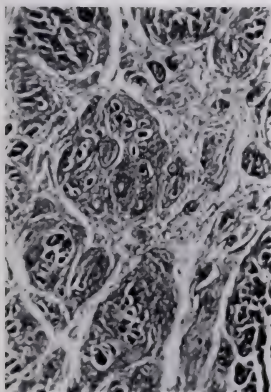


FIG. 4

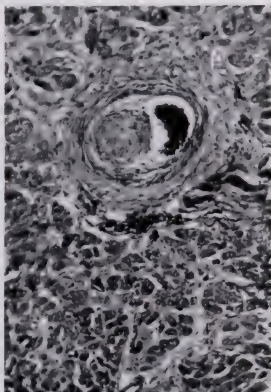


FIG. 5

FIG. 4. Myofibrosis in the wall of the left atrium (Mallory's aniline blue).
FIG. 5. Obstructed artery in the left atrium indicating atrial infarct (trichrome stain).

branches. The pulmonary artery main stem and the first branches were most severely involved with the sclerosis. This was a secondary and not very striking response to increased pressure associated with some contraction. We saw some areas of atelectasis which may have been related to the Kerley lines seen on the chest x-ray.

A primary lesion in the lung was easily excluded and we had to assume that the severe pulmonary congestion was related to some lesion in the heart. It was conspicuously enlarged and weighed 570 grams. The pericardial sac contained a small amount of fluid. Violin-string-like pericardial adhesions were seen over the anterior surface of the heart (Fig. 3). The right ventricle was very dilated. Both the right atrium and ventricle showed a moderately severe degree of hypertrophy associated with a widening of the tricuspid ostium which measured 17 cms., approximately 4 cms. in excess of the upper limit of normal. The tricuspid valve itself was entirely normal. The incompetence was obviously the result of dilatation causing a functional regurgitation. I do not know how much we can say about the presence of murmur but if a murmur was present, I would believe it could have been associated with the incompetence of the tricuspid valve. The myocardium itself on the right side failed to reveal any anatomic changes. The left atrium appeared dilated and large but not quite as large as the right. The mitral valve was entirely normal. A thrombus was found in the left auricle. As occurs in a long-standing thrombus, the morphologic evidence showed us granu-

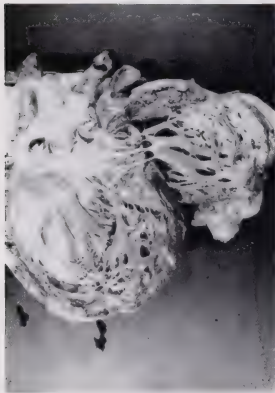


FIG. 6

FIG. 6. Anterior septal myocardial infarct with aneurysm formation.

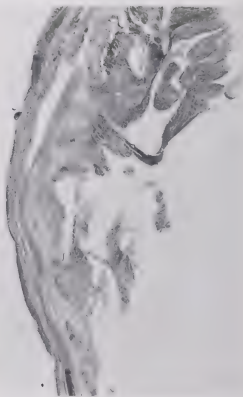


FIG. 7

FIG. 7. Extension of the aneurysm toward the right ventricle (Bernheim's syndrome) (Mallory's aniline blue).

lation tissue in the process of organization in the thrombus which was also in the process of disintegration. In the deeper layers of the atrial wall, we saw distinct myofibrosis (Fig. 4) and as we inspected the vessels we found them obstructed in this area (Fig. 5). I am more inclined to believe that this resulted from sclerosis of the atrial vessels with an atrial infarct and secondary thrombosis. We discovered the presence of a lesion in the septum which Dr. Friedberg has already predicted. It was an anteroseptal infarct with an aneurysm formation which bulged into the right ventricle; the Bernheim syndrome (Figs. 6 and 7). We also saw myofibrosis in the septum which was associated with distinct thickening of the endocardium in the right ventricle. The left descending branch of the coronary artery was completely occluded by an old thrombus. In places there was evidence of recanalization. Scattered areas of myofibrosis were present throughout the left ventricle (Fig. 8). The circumflex branch of the coronary artery was also almost completely obstructed and the right coronary artery too was obstructed but in some areas a lumen was seen. In the aorta there was severe arteriosclerosis and in both iliac arteries, which were both largely occluded, there were thrombus formation and aneurysms.

In summary, we had a patient with severe generalized arteriosclerosis involving the aorta, cerebral arteries, iliac arteries, splenic arteries and the coronary arteries, with obstruction of the left anterior descending and circumflex branches. This led, sometime earlier, to an arterio-septal myocardial infarction which resulted in an aneurysm producing possibly the Bernheim syndrome, and left ventricular failure. The left ventricular failure in turn led to left atrial dilatation with infarction and thrombus formation. This caused severe and progressive pulmonary congestion and right atrial dilatation. Both dilated atria compressed the esophagus. The right atrial dilatation was associated with hypertrophy of the right ventricle. Some compensatory mechanism for

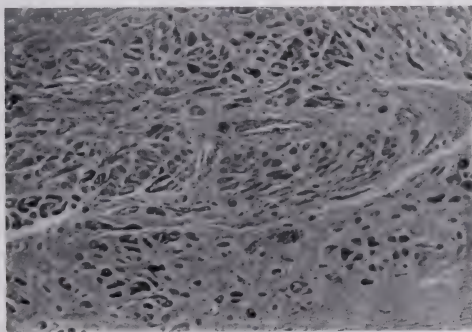


FIG. 8. Scattered areas of myofibrosis in the wall of the left ventricle (trichrome).

the pulmonary congestion developed with pulmonary arterial constriction which further increased the pressure upon the right ventricle. Pulmonary hypertension was not present and the right ventricle failed, producing the picture of the severe tricuspid incompetence with system congestion.

Final diagnosis: Anteroseptal myocardial infarction with a possible Bernheim syndrome and functional tricuspid insufficiency.

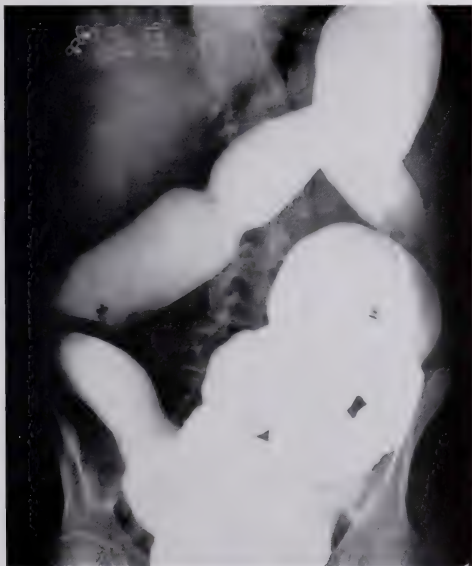
Generalized arteriosclerosis.

Radiological Notes

BERNARD S. WOLF

CASE NO. 101

This was the first admission of a 63 year old white female with the chief complaint of recurrent edema of the left leg over a period of two years. She had been treated by mercurial diuretics and fluid restriction. Associated with diuresis, she experienced severe weakness on several occasions and bouts of syncope. She was admitted for further investigation. The tongue was smooth and showed moderate pallor. There appeared to be an irregular right lower quadrant mass which was not tender. Pelvic and rectal examinations were unsatisfactory. The hemoglobin was 10.6 grams per cent. Six days after admission the mass in the right lower quadrant was not palpable. Sigmoidoscopy was negative. A barium



Case 101, Fig. 1A. Barium enema examination shows a "moulage" appearance of the right side of the colon, i.e., an effacement of all haustral and mucosal markings with normal or somewhat increased distensibility. Small sessile filling defects may represent "pseudopolyps" or adherent fecal material. At the beginning of this examination, there was a large quantity of fluid in the colon.



Case 101, Fig. 1B. After evacuation, there is considerable retention of barium especially on the right side of the colon which shows bizarre contractility. The terminal ileum (arrow) is somewhat more distensible than normally seen and mucosal features are effaced. The ileocecal valve is markedly flattened or, in effect, absent.

enema examination (Figs. 1A & 1B) showed an unusually distensible colon with obliteration of the normal haustral pattern, particularly in the right side of the colon and in the transverse colon. After evacuation, there was irregular contractility and retention of barium on the right side of the bowel. In the barium column, there was evidence of several small flat filling defects which suggested the possibility of small polyps but a second examination was not done for confirmation. Therefore, the possibility that these represented adherent fecal material cannot be excluded. The terminal ileum was seen after evacuation and also showed an obliteration of the normal mucosal pattern but normal distensibility.

The roentgen findings in this patient consist essentially of functional abnormalities including haustral effacement involving the right side of the colon as far as the splenic flexure. While an appearance such as this may be seen in "burnt-out" ulcerative colitis, the totally bizarre motor function and the variability of the picture suggests another possibility, namely, that the changes are the result of the use for many years of drastic irritant cathartics which have their action

mostly on the colon (1). The patient stated that she had been in the habit of taking cathartics daily for many years because of a presumed kink in her large intestine demonstrated on x-ray examination many years ago. There was no history of diarrhea at any time.

The patient was readmitted about one year later for a carcinoma of the thyroid. She had no abdominal complaints.

Final Diagnosis: "CATHARTIC COLON".

REFERENCE

1. HEILBRUN, N. AND BERNSTEIN, C.: Roentgen Abnormalities of the Large and Small Intestine Associated with Prolonged Cathartic Ingestion. *Radiology* 65: 4, 549, 1955.

CASE NO. 102

This was the second admission of a 38 year old female, known to have ulcerative colitis of many years duration. Three years prior to admission, an attempt was



Case 102, Fig. 1A. Barium enema examination shows changes of ulcerative colitis throughout the colon most marked in the transverse and descending colon. In the dilated cecum and ascending colon, there is a lobulated filling defect (arrow) which is sharply demarcated and appears to occupy the lumen.



Case 102, Fig. 1B. In the opposite oblique projection, the segmental pattern and elongated configuration of the filling defect are evident and are characteristic of loops of small bowel. The loops of bowel are relatively lucent not because they contain gas but by contrast with the surrounding barium. The caput coli is not involved in the intussusception; the cecum and ascending colon are dilated. None of the barium entered the small bowel.

made to close a rectovaginal fistula which had been present for many years. Post-operatively, the ulcerative colitis increased in severity and ileostomy was required. After the operation, the passage of mucoid material from the rectum once or twice daily continued and for several months prior to the second admission there had been more than a dozen per day preceded by abdominal cramps so that the patient was incapacitated. The ileostomy, however, functioned well. Physical examination was not contributory. Barium enema examination was performed (Figs. 1A, & 1B) and showed shortening of the bowel with obliteration of the haustral pattern and marked thickening of the mucosal pattern with ulcerations in numerous areas particularly on the left side. An unusual feature, however, was the presence in the cecum and ascending colon of lobulated filling defects which had the appearance of loops of small bowel, presumably intussuscepted distal ileum. The patient was operated upon and a total colectomy performed. The bowel showed typical changes of acute and chronic ulcerative colitis, and the intussusception of the excluded distal ileum into the

ascending colon was confirmed. The tip of the intussuscepted portion of the bowel was edematous and hemorrhagic.

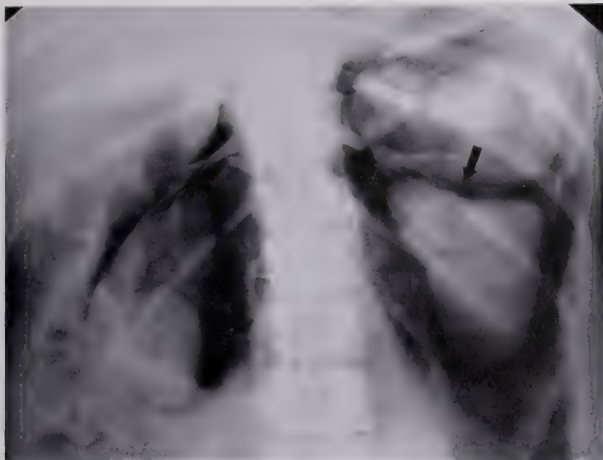
Intussusception of excluded ileum into the colon is uncommon. In this patient, apparently it was not associated with any acute symptomatology although it is possible that the ulceration of the intussusceptum contributed to this patient's persistent colonic discharge.

Final Diagnosis: INTUSSUSCEPTION OF EXCLUDED TERMINAL ILEUM.

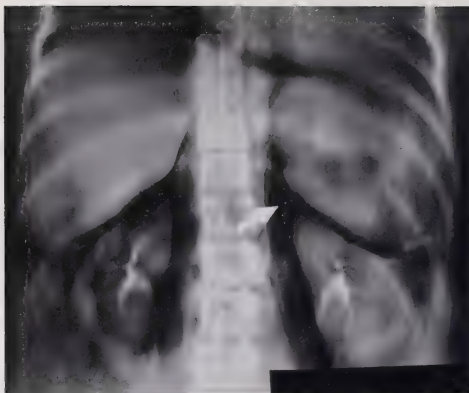
CASE NO. 103

This was the first admission of a 23 year old female who entered with the chief complaint of excess hair on the face and body since the age of nine. At the age of nine, normal menstrual periods started and breast development began at that time as well. There was no history of hypertension or diabetes but a fairly marked obesity had been present for some time. Examination on admission showed an obese female with hirsutism in the beard and moustache areas. There was dark hair over the front and back of the trunk, legs and arms. The pubic hair had male characteristics. The breasts were normal. The clitoris was enlarged to about twice normal size. The uterus could not be palpated, presumably as a result of the obesity. There were no adnexal masses felt.

Examination of the abdomen and retrorectal air insufflation combined with



Case 103, Fig. 1A. Retrorectal air insufflation demonstrates a large ovoid soft tissue density above the left kidney. The upper pole of the left kidney (arrow) is flattened and indented by this mass.



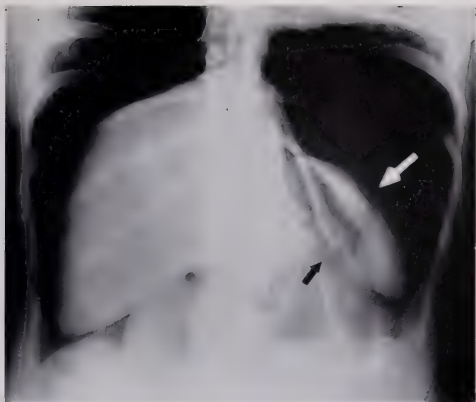
Case 103, Fig. 1B. Tomography after intravenous injection of opaque material shows the mass somewhat more clearly. It does not occupy the region of the left adrenal (arrow).

intravenous pyelography (Figs. 1A, & 1B) showed a large globular, homogeneous, soft tissue density lying above the upper pole of the left kidney and indenting the upper and lateral margin of this organ. It was felt, however, that the region of the left adrenal as well as that of the right adrenal were not remarkable and that the mass visualized was not related to the adrenal gland. Because of previous experience in similar cases and the failure to visualize the normal splenic contour it was felt that this mass represented an abnormally rotated and located spleen. Pneumoperitoneum was done (as part of a gynecogram) which demonstrated that this mass density was spleen which with gas in the peritoneal cavity, assumed a normal appearance in the PA projection (Fig. 2). Incidentally, the ovaries did not appear to be remarkable although there was a suspicion that the right ovary might be somewhat enlarged.

Chemical studies of endocrine excretion showed no abnormality. The 17 keto-steroid urinary excretion was within normal limits.

Exploratory laparotomy was performed on the basis that this patient might be suffering from the Stein-Levinthal syndrome. Wedge biopsies were taken from the ovaries which demonstrated follicular cysts. The spleen was observed and found to be of normal size and configuration.

The large size of the spleen in the antero-posterior projection as well as the flattening of the upper pole of the left kidney were apparently the result of an abnormal axis of the spleen, and the fact that it occupied a "pseudo-fossa" in the posterior abdominal wall. This appearance is unusual and the correct diag-



Case 103, Fig. 2. Pneumoperitoneum as part of a gynecogram shows a normal appearance, and mobility of the spleen (arrows).

nosis can easily be demonstrated by pneumoperitoneum when the normal mobility and configuration of the spleen are evident.

Final Diagnosis: "ECTOPIC" SPLEEN.

CASE NO. 104

This was the first admission of a 61 year old male with the chief complaint that three days prior to admission he experienced the sudden onset of crampy lower abdominal pain which extended towards both flanks. The pain was rapidly followed by abdominal distension and persistent vomiting. The patient was constipated but an enema yielded gas and a small amount of fecal material. He was considered to have a gastroenteritis or perhaps a renal calculus since an occasional red blood cell was found in the urine. The previous history revealed that ten years previously he had experienced occasional diarrhea after eating spicy foods and that he had suffered from Buerger's disease for many years. Thirty-five years prior to admission, he had undergone an appendectomy. Examination revealed an acutely ill male whose pertinent physical findings were confined to the abdomen which was rather markedly distended and tympanitic. No masses were palpable. Blood pressure was 130 80. Temperature was 101°F. Hemoglobin was 13.2 grams per cent. Total white count was 6,600 per cu. mm. with 58 per cent polymorphonuclear leukocytes including 28 per cent band forms. About four days after admission, when his temperature was normal, the white blood count was 11,000 per cu. mm, with 80 per cent polymorphonuclear leukocytes including 20 per cent band forms. The urine showed an occasional red and white blood cell.

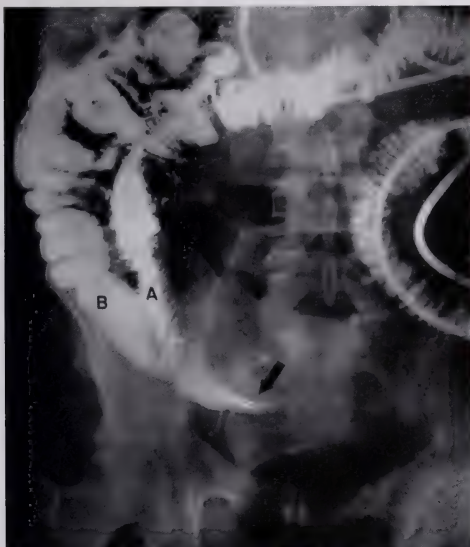


Case 104. Fig. 1A. Film of the abdomen taken shortly after the instillation of barium through the long suction tube shows no obstruction to the flow of barium but there are two loops of distal jejunum at the brim of the pelvis on the right side which are immediately adjacent and parallel to each other and which appear to form an acute angle at their junction. At this angulation, there is a suggestion of extrinsic pressure (arrow). The fold pattern at this site appears to be intact and there is no evidence of an intrinsic lesion of the visualized portions of the small bowel.

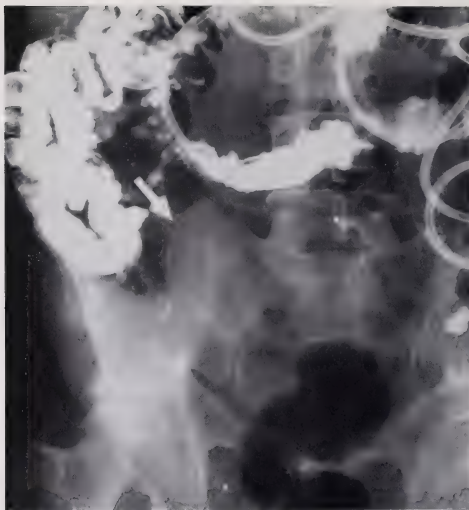
Roentgen examination of the abdomen showed considerable distension of multiple loops of small bowel, but fecal material could be seen outlining the colon which did not appear to be distended. With the passage of a long suction tube, the distended loops of small bowel were rather rapidly decompressed. The clinical diagnosis was partial small intestinal obstruction, presumably the result of adhesions from the previous appendectomy. This appeared to be confirmed by the roentgen findings. An attempt to remove the suction tube, however, resulted in another attack of severe pain and abdominal distension despite the fact that with the tube *in situ* there had been no pain and the patient had been moving his bowels normally. The Cantor tube was then replaced. Barium was instilled through the Cantor tube for further investigation and serial examination of the abdomen performed. This demonstrated an acute angulation in the distal jejunum in the right lower quadrant (Figs. 1A, 1B, 1C). The afferent and efferent loops to the site of angulation appeared to be rather fixed in position. The mucosal pattern of the small bowel at the angle appeared to be intact although com-

pressed. On two of the films there was evidence of extrinsic pressure, perhaps by a mass. Despite the angulated site, there was no remarkable obstruction to the flow of barium through the small bowel. A definite roentgen diagnosis was not made from this examination although it appeared to be consistent with adhesions in the right lower quadrant.

The patient underwent exploratory laparotomy and a tumor about nine cm in its greatest diameter was found attached to the jejunum by a pedicle. The tumor and the adjacent portion of small bowel were resected. The tumor mass was well encapsulated and, on section, showed evidence of necrosis and hemorrhage with cystic spaces. The mucosa of the small bowel was unremarkable



Case 104. Fig. 1B. Examination about one hour after figure 1A shows somewhat similar findings but the junction of the afferent loop of small bowel (A) and the efferent loop (B) shows a suggestion of an arcuate configuration indicative of extrinsic pressure (arrow). In the region of the angulation, there is no discrete soft tissue mass but the possibility of a mass is suggested by the failure of any bowel to occupy the adjacent region. The air containing viscus some distance above this site and immediately medial to loop A represents a portion of redundant sigmoid (as demonstrated on barium enema examination).



Case 104, Fig. 1C. Re-examination three hours after figure 1B shows practically all of the barium to have traversed the site of angulation in the small bowel. An arcuate indentation (arrow) of a gas containing loop in the right lower quadrant, probably the redundant loop of sigmoid, is evident and suggests an extrinsic mass.

except for a small dimple at the site of the pedicle. Microscopic examination showed the tumor to be a myoma with extensive hemorrhagic infarction. There was no evidence of malignant change.

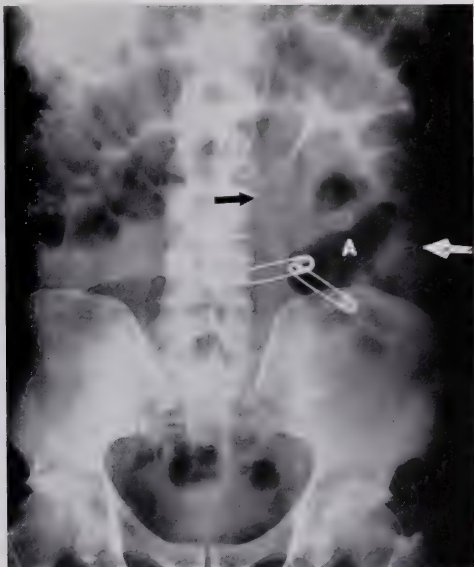
The correct diagnosis in this case was missed despite experience with a very similar case (Case No. 100). The roentgen findings of acute angulation of the bowel producing a V-shaped appearance, with partial intestinal obstruction, and evidence of extrinsic pressure by a soft tissue mass, as well as the clinical picture of an acute lower abdominal episode, inflammatory but not infectious in nature, are features which suggest the correct diagnosis.

Final Diagnosis: LARGE PEDUNCULATED MYOMA OF THE SMALL BOWEL WITH HEMORRHAGIC INFARCTION.

CASE NO. 105

This was a 67 year old male who three days after colotomy and polypectomy of the descending colon, developed gastric retention, fever and moderate abdominal distension. There was a slight salmon pink discharge from the drainage

site. An obstructive series was ordered because of the possibility of a loop adherent at the wound site. The conventional examination of the abdomen for intestinal obstruction was done (Fig. 1). This demonstrated a short, arcuate, somewhat distended loop of bowel, presumably small bowel, on the left side of the abdomen in relationship to the abdominal incision and drains. However, close observation of the film demonstrated very clearly that the suture line, as indi-



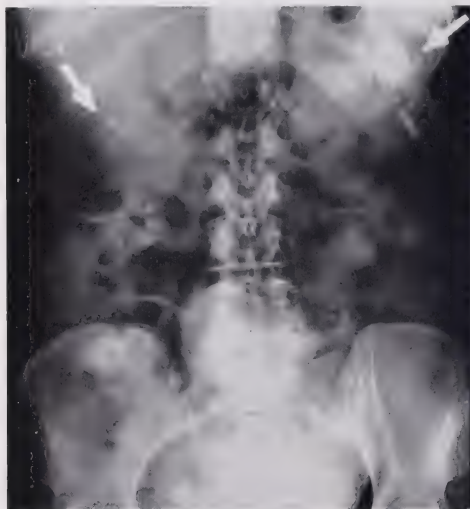
Case 105. Fig. 1. Examination of the abdomen shows an arcuate, rather markedly distended loop of bowel (A) on the left side of the abdomen which has an irregular configuration. There are multiple, considerably distended loops of small bowel in the upper abdomen proximal to this site. The location of this loop, as indicated by safety pins within the drains, is related to the abdominal incision. Moreover, the suture line is marked by metallic sutures which careful examination shows to line up in two rows, the more proximal row (upper arrow) medially located and the lower group (lower arrow) laterally located. The separation of the two portions of the suture line is indicative of disruption. The loop of bowel designated as A in the figure was demonstrated to be directly underneath the skin in a tangential view of the abdomen. This special view, however, might not have been taken unless the correct diagnosis was suspected.

eated by the row of metallic sutures, showed a wide separation in its mid-portion directly over the dilated loop. The diagnosis of a subcutaneous evisceration could then be made and this was easily confirmed by a tangential view of the abdomen. The wound of the patient was opened and a loop of small bowel found which was replaced. After this, the patient did well.

Final Diagnosis: POST-OPERATIVE SUBCUTANEOUS EVISCERATION DEMONSTRATED BY DISRUPTION OF METAL SUTURES.

CASE NO. 106

This was the first admission of a 64 year old female with the chief complaint of a growth in the umbilicus. The menopause had occurred 12 years previously. There was no history of post-menopausal bleeding. She had undergone routine



Case 106, Fig. 1. Examination of the abdomen shows a huge, apparently lobulated calcified mass in the pelvis extending into the upper abdomen in the mid-line and on the right side. The diffuse calcification gives a homogeneous hazy density to the calcified areas, but closer observation shows that this is the result of innumerable punctate densities which are not entirely confluent. Moreover, high on the right and left side of the abdomen (arrows), similar conglomerate punctate calcifications are noted. This is the typical picture of papillary cystadenocarcinoma of the ovary with peritoneal implants.

medical examinations including pelvic examination twice a year until two years prior to admission. These were said to have been negative.

Examination on admission showed an obese female in no distress. In the umbilicus there was a two cm. nodular, discolored, non-tender mass. A large hard irregular mass was felt extending from the pelvis upwards into the abdomen. Clinical diagnosis was probable ovarian carcinoma with peritoneal implants.

Roentgen examination of the abdomen (Fig. 1) showed a huge mass or masses occupying the lower abdomen throughout which there were numerous calcifications which gave a homogeneous hazy density to the entire area. This hazy density, however, was not uniform; the calcifications actually consisted of innumerable discrete punctate deposits. In addition to the lower abdominal calcifications, high in the abdomen on both the right and left sides, there were additional areas of similar conglomerate punctate calcifications. The roentgen diagnosis was huge papillary cystadenocarcinoma of the ovary with diffuse peritoneal spread. The type and extent of the calcification is quite typical of this condition. Calcification within uterine fibroids is less extensive, usually more gross and amorphous, rather than generalized and punctate. Similar calcified areas at a distance from the main mass do not occur with fibroids.

The patient was explored and generalized carcinomatosis found, due to bilateral papillary cystadenocarcinoma of the ovaries. The tumor tissue was in part gelatinous but in considerable part consisted of solid, granular, gritty tissue. Microscopic examination showed very extensive psammoma body formation.

Final Diagnosis: PAPILLARY CYSTADENOCARCINOMA OF THE OVARIES WITH PERITONEAL IMPLANTS DEMONSTRATED BY EXTENSIVE PSAMMOMA BODY FORMATION.

CASE NO. 107

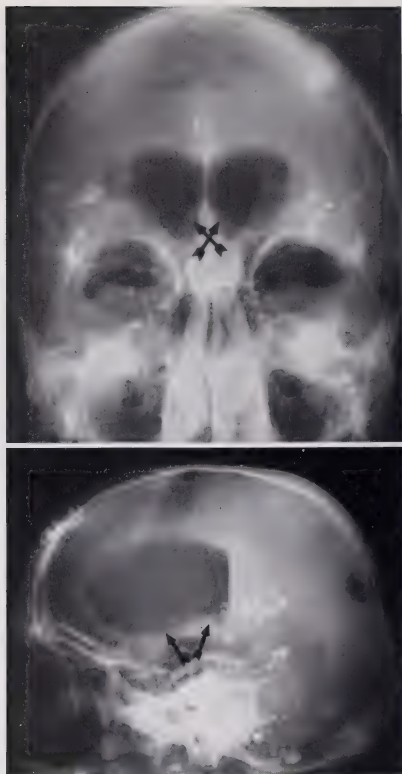
SUBMITTED BY DRs. CHARLES M. NEWMAN AND MANSHO T.
KHLNANI

This was the third admission of a 58 year old right handed woman admitted because of difficulty in walking of ten years duration. Her balance was poor and she had a sensation of falling to the right.

Her first admission in 1948 was for progressive weakness and urinary incontinence. A diagnosis of multiple sclerosis was entertained at that time.

Her second admission in 1951 was for the complaint of unsteady gait, and again a diagnosis of multiple sclerosis was made.

Physical examination revealed a well oriented, somewhat dull individual. Visual acuity was diminished, particularly in the left eye. The visual fields and optic fundi were normal. There was a transient nystagmus on left lateral gaze. The gait was slow, broad based, and ataxic, with a tendency to fall in all directions. There was no significant weakness of the lower extremities. The deep tendon reflexes were two plus and symmetrical. Caloric tests were normal. Stereognosis was normal.



Case 107, Fig. 1A. Pneumoventriculogram antero-posterior view demonstrates a smoothly contoured mass three cm in diameter, symmetrically indenting the inferior medial aspect of the first part of the body of both lateral ventricles (arrows). The lateral ventricles are markedly dilated but not displaced. The third ventricle is not filled with air. Residual pantopaque from the previous myelogram is seen in the Sylvian fissures and along the base of the brain.

Case 107, Fig. 1B. Pneumoventriculogram: brow up—lateral view again shows the smoothly contoured mass indenting the inferior medial aspect of the first part of the body of the markedly dilated lateral ventricles (arrows).

The laboratory findings were normal except for a spinal fluid pressure of 200 mm and a protein content of 46 mgms per 100 cc Wasserman and colloidal gold curve were negative. Electroencephalogram showed left frontal slowing with shifting bursts.

On the presumption that the patient had spinal cord disease, a pantopaque myelogram was done which revealed some ridging in the cervical spine. A pneumoencephalogram revealed markedly dilated lateral ventricles without gross displacement, but repeated attempts to fill and visualize the third ventricle were unsuccessful. The fourth ventricle appeared normal. A right carotid angiogram revealed a wide arching of the anterior cerebral artery consistent with hydrocephalus. The deep cerebral veins were not filled in any of the venous phases suggesting the possibility of compression by a regional mass.

A pneumoventriculogram (Figs. 1 A, 1 B) revealed a symmetrical indentation by a mass approximately three cms. in diameter on the inferior medial contour of the markedly dilated lateral ventricles from the level of the foramen of Monro backwards. The third ventricle was not filled with air.

The diagnosis of a mass in the anterior third ventricle was made and because of its smooth contour and long clinical course the possibility of a colloid cyst was suggested.

A right-sided craniotomy was done and, through a cortical incision in the middle frontal convolution, the frontal horn was opened and a pale, bluish green cystic mass was seen to bulge through the dilated foramen of Monro. The contents of the cyst were too viscous to aspirate. An incision through the capsule revealed thick stringy mucoid material. The capsule was carefully excised.

The greatest improvement two months post-operatively appeared to be in walking. Most of the other signs and symptoms persisted.

A colloid cyst of the third ventricle is an uncommon benign lesion presumed to be developmental in origin. The course is usually slowly progressive, although symptoms and signs of increased intracranial pressure may appear suddenly. Because of the prolonged course and the inaccessibility of the lesion, the prognosis is ordinarily quite poor, although remarkable improvement after surgical intervention has been reported.

Final diagnosis: COLLOID CYST OF THE THIRD VENTRICLE.

Surgical Techniques

1. THE USE OF THE LEFT COLON FOR ESOPHAGEAL REPLACEMENT

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The most common cause for failure of esophageal anastomosis is leakage at the anastomotic site. The breakdown at this site can be avoided if the blood supply is maintained and there is no tension at the suture line. It is with this in mind that the use of the left colon for esophageal replacement is being utilized at The Mount Sinai Hospital. This procedure also avoids the morbidity associated with those techniques in which the stomach is moved into the thorax. It is preferable to use the left colon rather than the right because its natural position is high against the left diaphragm. The splenic flexure may, at times, be as high, vertically, as the mid-thoracic esophagus. This tendency to anatomical approximation is of advantage in providing ease of anastomosis.

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The section on Surgical Techniques is one of a series prepared by the Department of Surgery. Some of the techniques described are original, others are of long-established application, some with modifications found useful here. The descriptions afford a concise review of techniques currently utilized at The Mount Sinai Hospital, New York.

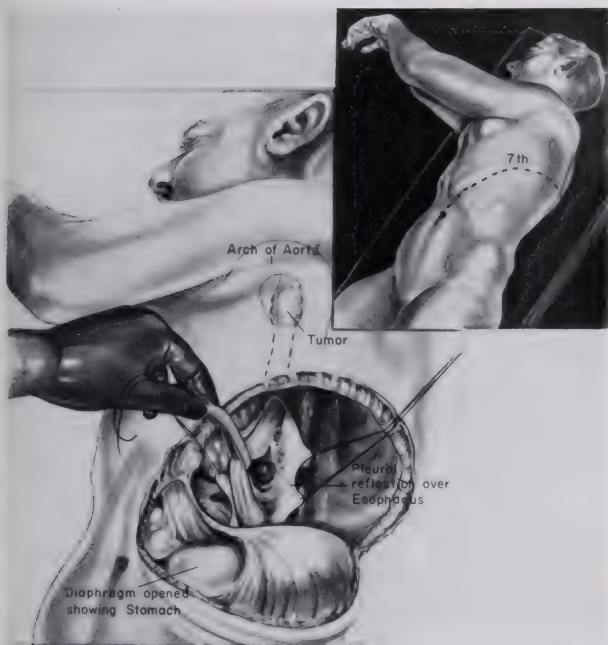


Fig. 1. Insert showing incision. The patient is lying on his right side. The larger illustration shows the beginning of the esophageal dissection.

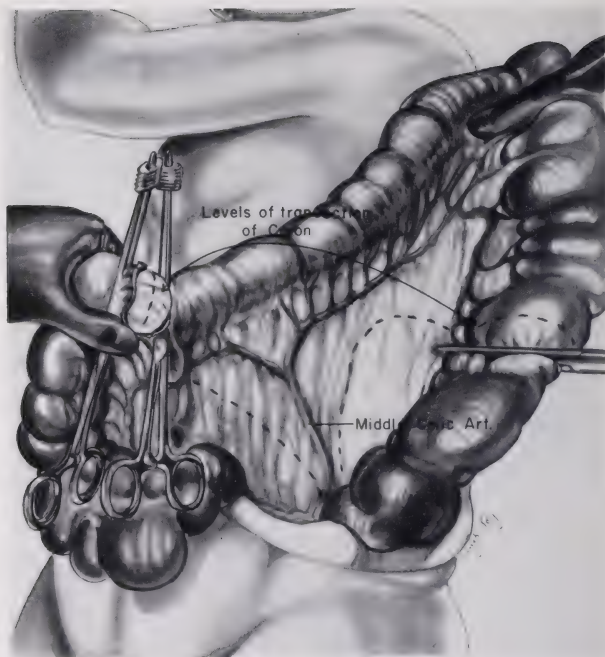


Fig. 2. The entire transverse colon, splenic flexure, and descending colon are freed. The mid-colic artery is outlined, and the mesocolon incised along the line shown. Care is taken to preserve the arterial arcades along the mesenteric border of descending colon. The amount of descending colon utilized will depend upon the length of colon required. In this illustration the right transverse colon is being transected between aseptic technique clamps.

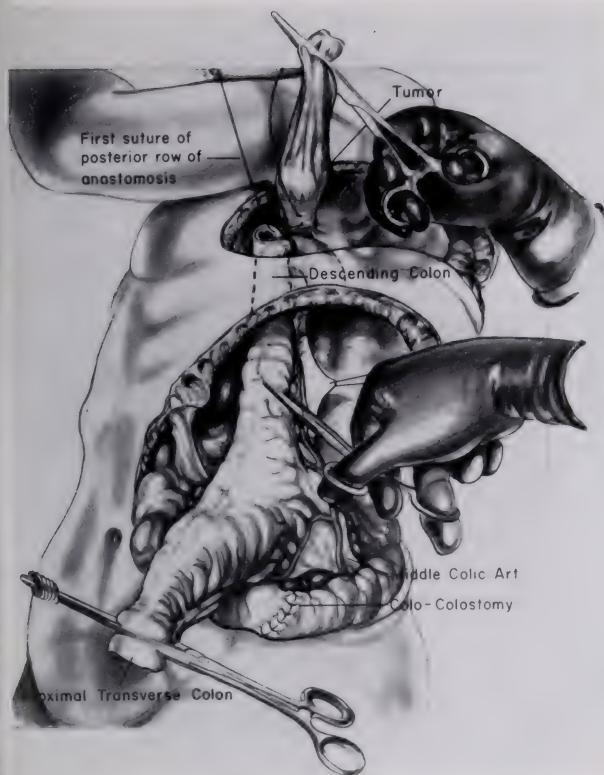


Fig. 3. The loop of colon is in position for anastomosis to the stomach and the esophagus. Note the absence of tension and the position of the mid-colic artery. That portion of the colon derived from the descending colon is anastomosed to the esophagus, while the transverse colon is anastomosed to the stomach.

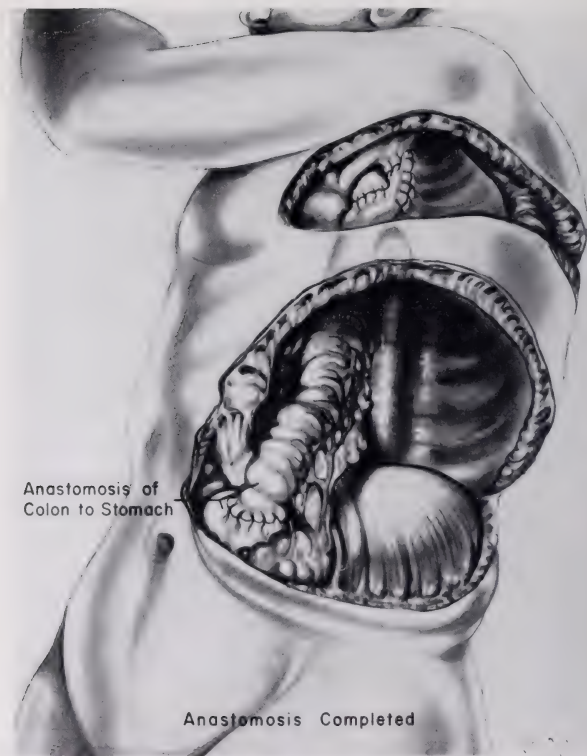


Fig. 4. The anastomotic operations are now completed. The pleural reflections are used to re-enforce and cover the anastomosis of the esophagus. The colon is allowed to transverse the diaphragm through the former esophageal hiatus and the diaphragm is then closed.

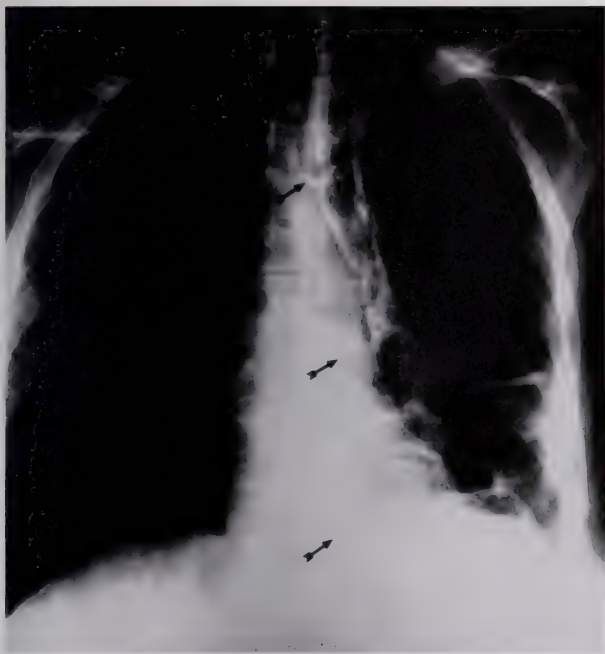


Fig. 5. Roentgenogram of a patient with a segment of left colon utilized for esophageal replacement. Arrows point to the colon containing barium.

Abstracts

*Experimental Acute Glomerulonephritis in the Rat. Electron and Light Microscopic Studies.** Jacob Churg, M.D., Edith Grishman, M.D., and Willy Mautner, M.D. (From the Department of Pathology and the Cell Research Laboratory). Presented November 9, 1959.

Masugi-type nephritis was produced in rats by means of a single injection of anti-kidney rabbit serum. Animals were sacrificed at intervals from two hours to six weeks and the renal changes were studied by means of light and electron microscopy.

The experimental illness could be divided into two phases. During the first three days the cellular components of the glomerulus showed considerable damage. There was swelling of the epithelial and the endothelial cytoplasm and nuclei, formation of vacuoles, edema of the mitochondria, and "fusion" of the epithelial foot processes. In the severely affected animals the foot processes disappeared completely and the capillaries were obstructed by the swollen endothelial cells and "hyaline" (fibrin) thrombi. During this phase the animals developed albuminuria, oliguria and sometimes fatal uremia. In the second phase (3 to 15 days) tissue edema and albuminuria reached the maximum level; abnormalities appeared in the serum electrophoretic pattern. The cellular changes tended to regress, the foot processes were present and the capillaries were patent, but, at the same time, the capillary basement membranes became markedly (up to 3 times) thickened, frayed and split into two or more layers. After 15 days albuminuria and edema receded and the glomerular changes regressed. In many animals, however, the basement membrane remained thickened and split, and an increased number of cells and "fibers" appeared in the widened intercapillary spaces. Administration of cortisone tended to lessen the severity of both the cellular and the basement membrane changes.

Demonstration of Gamma Globulin in Experimental Vascular Lesions.† Goroku Ohta, M.D., Seymour Cohen, M.D., and Edward J. Singer, Ph.D. (From The Department of Pathology). Presented November 9, 1959.

In some instances of human and experimental arteritis, gamma globulin has been demonstrated by fluorescence microscopy (Coons technique). Using that technique, such lesions, often attributed to hypersensitivity, were compared with vascular lesions accompanying hypertension. Both human cases and experimental animals (rats and rabbits) were used. This report is based mainly on experimental lesions.

A. Necrotizing arteritis, localized predominantly in the splanchnic vessels, was produced in rats by unilateral nephrectomy followed by administration of DocA acetate and silk-wrapping of the contralateral kidney.

B. Granulomatous angiitis, localized predominantly in the coronary vessels,

* Supported by Research Grant (A-918), National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Bethesda, Md., and a Grant from the Northern New Jersey Chapter of the National Kidney Disease Foundation.

† (Supported by a grant from the Block Foundation).

was produced in rabbits by three injections of horse serum. In some of the animals these were preceded by unilateral nephrectomy.

Vascular lesions were studied by conventional staining methods and by staining cryostat sections and sections prepared by the freeze substitution technique with fluorescein-labelled anti-gamma globulin.

In the rat, fluorescence was observed in damaged smooth muscle of the media of small arteries and arterioles showing fibrinoid necrosis; it was absent in undamaged vessels. It was partially blocked by unconjugated anti-gamma globulin, and could not be blocked by normal rabbit gamma globulin, suggesting that fluorescence was specific for rat gamma globulin.

Granulomatous vascular lesions in rabbits showed a more diffuse but less brilliant fluorescence extending throughout the vessel wall and into the perivascular connective tissue.

These findings can be explained by one of several assumptions: (a) diffusion of gamma globulin into the damaged area; (b) specific binding of gamma globulin by antigenic substances (injected foreign protein or denatured tissue protein). These alternatives will be investigated.

Diagnosis of Pheochromocytoma by Determination of Urinary 3-Methoxy, 4-hydroxymandelic acid. Stanley E. Gitlow, M.D., Sarah Khassis, M.D., Gerald Cohen, M.D., and Milton Mendlowitz, M.D. (From the Department of Medicine). Presented November 9, 1959.

The metabolic pathways for the degradation of epinephrine and norepinephrine have been clarified by the recent investigations of Armstrong et al., Axelrod, and Sjoerdsma et al. These studies suggest that the diagnosis of pheochromocytoma may be facilitated by analysis for the phenolic compounds: 3-methoxy, 4-hydroxymandelic acid (VMA), or 3-methoxy, 4-hydroxyphenylethanolamine (NM) and its N-methylated congener (M), which are the metabolic biproducts of catecholamine metabolism.

Procedures for analysis of NM and M are not as well perfected as M.D. Armstrong's unpublished technique for determining VMA, which was used with minor modifications: acid hydrolyze a volume of urine equivalent to 0.5 mg, creatinine, extract with ethyl acetate, evaporate, dissolve in ethanol, re-concentrate, spot on corner of 1' x 1' square of filter paper and chromatograph bidirectionally in isopropanol:water:NH₃ (40:9:1) and benzene:propionic acid:water (20:14:1). Color development with diazotized p-nitroaniline yields a purple spot for VMA with R_f values of .27 (isopropanol:NH₃ system) and .15 (benzene:propionic acid system). Comparison of the unknown with VMA standards simultaneously spotted on each chromatogram yields a reproducible accuracy of plus or minus 15 per cent.

Twenty subjects with no evidence of pheochromocytoma excreted one to three μ g. VMA/mg of creatinine. Urine samples from 24 patients with surgically proven pheochromocytomata revealed 7.5 to 40 μ g. VMA/mg of creatinine (4.4-187 mg VMA/24 hrs.) and 0.08 to 6.9 μ g catecholamines/mg of creatinine (83-5500 μ g catecholamines/24 hrs). Urine specimens from patients with pheochromocytoma

contained 5 to 25 times as much VMA as catecholamines. The relative ease and reproducibility of VMA urinary analysis along with its diagnostic accuracy make it a useful procedure for the diagnosis of pheochromocytoma. [Abstracted in Clin. Res. Proc., April-May, 1959. More detailed report will be available in the J. Clin. Invest., 1960.]

Importance of Potassium Shift and Total Bicarbonate During and Immediately Following Total Body Perfusion. I. Krasna, M.D., H. Baens, M.D., I. Kreef, M.D., M. Shuster, M.D., and I. D. Baronofsky, M.D. (From the Department of Surgery).

Metabolic and electrolyte studies were carried out on a group of dogs subjected to prolonged extracorporeal circulation (one hour). The Kay-Cross oxygenator, using two per cent carbon dioxide and 98 per cent oxygen was used. 25 cc of sodium bicarbonate solution (22 mEq) were added to the oxygenator for every 20 minutes of perfusion. Electrolytes, pH, Carbon dioxide content, bicarbonate content, and $p\text{CO}_2$ were measured preceding, during, and following the run. Acidosis, with a decrease in blood bicarbonate developed when smaller amounts of bicarbonate were given. Some animals developed acidosis despite adequate perfusion and adequate amounts of bicarbonate. Acidosis, manifested by a drop in pH, was preceded by a drop in total bicarbonate at a time when the pH was still normal. Total bicarbonate is a more accurate indication of impending acidosis than pH values. Depletion of total bicarbonate will result in uncompensated acidosis.

A decrease in serum potassium to as low as 1.8 and 2.4 mEq was noticed in most cases three to five hours postoperatively. In these cases, acidosis was corrected during perfusion with bicarbonate, and the postoperative pH values were normal or alkalotic. It is suggested that a hyperkalemia develops during the acidotic phase, and potassium enters the cells during correction of this acidosis with bicarbonate, causing a hypokalemia. Elevated pH values were associated with low serum potassium values, and low pH values were associated with elevated serum potassium values.

**DIAGNOSTIC ROENTGENOLOGY
OF THE DIGESTIVE TRACT
WITHOUT CONTRAST MEDIA**

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Preface

The great value of simple films of the abdomen in acute abdominal conditions is well known and well documented in the roentgen and surgical literature. In contrast there is relatively little information pertinent to more chronic diseases of the gastro-intestinal tract unassociated with gross obstruction or perforation. Most radiologists are aware that such lesions can occasionally be recognized on simple films of the abdomen, that is, without the use of opaque media for the demonstration of selected regions. It is possible that this approach began more or less as a "trick" and there is no doubt that the recognition of a carcinoma of the colon or of the stomach from a simple film of the abdomen at a conference etc., may seem to be a feat of extraordinary insight, if not of unusually good luck. When, however, this question was systematically investigated by collecting cases in retrospect, it was found, admittedly somewhat to our surprise, that findings were often present on simple films which had been overlooked. It was possible within a short period of time to collect a considerable number of such cases. It was thought at first that this material might be reported and illustrated in the form of an atlas which would demonstrate the deviations from the normal which turned out to be of significance on further investigation by conventional methods. However, it was soon evident that this method of presentation was not basically informative for a rather obvious reason; the range of the normal was not well known or easily described. There are innumerable appearances on simple films of the abdomen in clinical practice which cannot be considered to be "perfectly" normal but which nevertheless on subsequent examination turn out to be of no diagnostic importance. An atlas which would demonstrate all normal as well as abnormal appearances turned out to be impractical. As a result, it was necessary to consider in greater detail the basic physical, physiological and pathological processes involved in an effort to establish generally applicable basic principles for the identification of significant abnormalities. It is not claimed that this more fundamental approach has been completely successful in separating the wheat from the chaff but the ideas described in the text appear sufficiently sound to permit further progress. As a result, the original plan of preparing an atlas has been considerably modified. The bulk of the text presents principles rather than detailed roentgen findings in specific cases. The roentgen features of diagnostic import do not depend on the type of contrast material, that is, whether gas or barium. No attempt is therefore made to describe all the possible roentgen findings of individual lesions. In several conditions, features were noted on simple films which were not as clearly evident on conventional examinations and an attempt to describe these additional findings is also made in the text. The conditions illustrated include the common disease states. A large number of miscellaneous conditions occasionally evident on simple films are not included in the current presentation.

The illustrations included in this monograph were selected from a large variety of examinations, not only simple films of the abdomen. In each case,

however, the examination requested was not pertinent to the site of disease and the area of interest was not opacified by barium or other opaque medium. In most instances, the type of examination, while not specified, is evident in the illustration, for example, a barium enema or an intravenous pyelogram although the lesion was located in the stomach etc.

Apology must be made to an unknown number of authors for the fact that the bibliography is quite scanty. To some degree, this is attributable to the fact that much of the material which might have been included if its existence were known consists of isolated illustrations in articles or texts which primarily present other topics. It is likely that at one time or another many of the features described in this monograph have been illustrated elsewhere. Any claim for originality is based only on additional emphasis of the diagnostic potentialities and a more systematic approach.

The authors have had considerable assistance in the preparation of this monograph from a large number of individuals, too numerous to be individually mentioned. The contribution of Dr. Joan Eliasoph to the section on ulcerative colitis is gratefully acknowledged. Several cases have been furnished by friends and colleagues to whom we would like to express our appreciation. These include Dr. Joan Eliasoph, Dr. Daniel Blum, Dr. Abraham Melamed and Dr. Herman Zuckerman. We are particularly indebted to Miss Molly Nadelman for the preparation of the manuscript and to Mr. John Tanczos for the high quality of the illustrations. We are also indebted to Dr. Lester Tuchman and the editorial staff of the Journal of The Mount Sinai Hospital for their encouragement and help.

It is the belief of the authors that careful study of abdominal films will prove to be an increasingly useful diagnostic tool. It is true that most of the illustrations in this monograph have been selected in retrospect, sometimes many months after the correct diagnosis was made. It is not the claim of the authors that these findings were obvious originally. It is hoped, however, that, by a study of collected material, we have learned to recognize similar current cases. The authors are confident that their personal diagnostic ability has been increased by this investigation, and harbor the hope that this monograph will furnish in a relatively painless fashion and within a short period of time similar experience to others.

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NOTE ON CONVENTIONS USED IN THE LEGENDS FOR THE ILLUSTRATIONS

In the majority of illustrations, the legend specifies the position of the patient when the film was taken, that is, prone, supine or erect. In each instance, however, the film is presented for viewing as if the reader is looking at the front of the patient, that is, the right side of the patient is to the left of the reader and vice versa. In the descriptive portions of the legends when "right" is mentioned, reference is being made to the *right* side of the patient and not to the right side of the reader. Similarly, the terms "medial" and "lateral" refer to the mid-line of the patient. The reproductions have the same tones as the original film, that is, a black area in the original film is also black in the illustration. In many of the legends, an "increase in density" is mentioned. This refers to an area in the illustration which is *whiter* than would be anticipated. Areas in the illustrations and in the original film which are blacker or darker are referred to as more "lucent" regions. This method of designation is consistent with the degree of absorption of the x-ray beam in the various portions of the body, that is, a whiter area ("increase in density") refers to an area of greater x-ray absorption in the body and a darker area ("decrease in density") refers to an area of diminished x-ray absorption. The term "density" used in this fashion does *not* refer to the physical density of the film.

CHAPTER ONE

*General Principles**

As a result of sixty years of roentgen examination of the gastrointestinal tract with contrast media, a huge amount of information of inestimable clinical value has been obtained. The usefulness of the simple, plain, or so-called preliminary film of the abdomen (1-4) in the diagnosis of intestinal obstruction and for the demonstration of free gas in the peritoneal cavity is well known. It remains, however, to determine how much information can be obtained from simple films of the abdomen in diseases of the gastrointestinal tract which are not associated with significant obstruction or with perforation. Clearly, this type of examination for this purpose will have severe limits but these limits have not been sufficiently explored. Offhand, it might appear superfluous to attempt to obtain information diagnostic of intrinsic lesions of the gastrointestinal tract from simple films since these conditions can be well demonstrated by conventional methods, specifically barium meal or barium enema examinations. There are, however, many occasions in clinical practice in which the site of primary disease is not clear originally and a variety of relatively impertinent roentgen examinations which happen to include the gastrointestinal tract or portions of it are more or less incidentally or accidentally obtained. In other instances, the clinical features appear to implicate other areas and work-up directed at the correct site may be inordinately postponed. The findings on a simple film of the abdomen may therefore be of considerable importance in directing attention immediately to the primary site of disease. There is little doubt that under most circumstances the clinician is well aware of the area to be investigated and that diagnostic contributions from a simple film may not be of significance. However, in current clinical practice, films of the abdomen are taken in such huge numbers that, although the yield on a percentage basis may be quite small, in absolute number the contribution may nevertheless be substantial. Moreover, experience in this field has indicated that a considerable number of patients with disease of the gastrointestinal tract show some changes, in some cases minimal, in others obvious, on simple films of the abdomen. Observations through the "retrospectroscope" have often demonstrated findings which should not have been overlooked. These findings are considerably more difficult to interpret in most cases than in conventional barium meal or barium enema examinations and often an exact anatomic diagnosis cannot be made. However, the presence of an abnormality deserving further investigation can be detected. In some conditions, diagnostic features may be present on simple films of the abdomen which are obscured or effaced by conventional methods of examination which necessarily involve the application of an artificial stimulus in an artificial manner. This is true for example in ulcerative colitis and in some cases of

* Figures for this chapter appear on page 116 et seq.

benign peptic ulcer of the stomach. On any film of the abdomen, there is truly a huge amount of information potentially available of a physiological or pathological-physiological nature which at the present time is difficult to extract because of limitations in basic knowledge.

Efforts to study the gastrointestinal tract on simple films of the abdomen are complicated by the large number of apparently random and unpredictable appearances which may be seen because of irregular distribution of fluid and gas within various portions of it. Moreover, films of the abdomen are taken under a variety of circumstances often after withholding food or after some type of preparation including use of cathartics or enemas. Many patients, particularly those in the hospital, are under the effects of a variety of medication which influences the appearance of the gastro-intestinal tract. Moreover, contrast media administered for radiographic purposes, for example, intravenous pyelography or cholecystography, also act on the gastrointestinal tract to produce variations from a normal or resting state. Fortunately, from a practical point of view, it is not necessary in order to obtain useful diagnostic information to understand in ultimate detail how all appearances are produced. In this field as in so many others, the radiologist can develop a body of empirical information which he uses to recognize deviations of clinical importance. At the start of such an effort, when films of the abdomen are scrutinized closely with a high index of suspicion, the number of "unusual" appearances is quite large, and numerous unnecessary contrast examinations may be ordered. With increasing experience, the number of such "unusual" appearances diminishes as the range of normal under circumstances of actual practice is delineated. As a matter of fact, most of the totally bizarre appearances do not turn out to be of organic nature but indicate a temporary functional state. Many radiographic examinations include multiple films of the abdomen, for example, pyelography, and the transient nature of such changes can therefore be recognized. It is characteristic of an organic lesion that the findings persist on serial films. It is essential to approach the problem from a positive point of view, that is, not only to recognize the peculiarity of a particular gas-fluid configuration, but to search for specific roentgen features indicative of an organic lesion. The purpose of this presentation is to emphasize positive features, namely, those which are useful in arriving at a specific diagnosis.

The conventional point of view in examining a radiograph of the abdomen is to observe the kidney outlines, the outlines of the spleen and liver as far as they can be seen, the psoas margins, the bones included in the examination and to search closely for abnormal calcifications or coneretions. Gas and fluid in the intestinal tract are often considered only obstacles in viewing these features. However, for our present purpose we are primarily interested in those structures which occupy the peritoneal cavity, specifically the stomach, the small bowel, and the colon. Gas and fluid within these hollow viscera as well as the fat around and adjacent to them are the features of specific interest. A view in depth of these abdominal structures must be practiced despite the fact that relatively few structural details may be visible. These viscera completely fill the peri-

toneal cavity; there are no "unfilled" or empty areas. On close observation there is rarely any portion of a radiograph of the abdomen except for the regions of the solid viscera which shows a completely homogeneous density. The normal size, configuration and location of the stomach, loops of small bowel, the colon and the various peritoneal extensions and reflections must be clearly understood and kept in mind. These basic anatomical features will not be repeated here in detail. It is necessary to recall, however, that the peritoneal cavity occupies only the anterior portion of the abdomen and that ordinarily it is somewhat ellipsoidal in cross section with the spine and the paraspinal structures protruding into it posteriorly in the mid-line. The length of a segment of bowel in the antero-posterior direction, that is, in the sagittal plane, is therefore distinctly limited and the long axes of the hollow viscera lie adjacent to the frontal plane. The bulk of the viscera lie lateral to the mid-line in the lumbar gutters. Displacement of these mobile viscera from the mid-line is exaggerated when the patient lies in the prone position. Since the posterior wall of the peritoneal cavity is relatively rigid, an increase in the volume of the peritoneal contents requires protrusion of the anterior and antero-lateral portions of the abdominal wall. Unfortunately it is very difficult to judge the thickness of the abdomen from an antero-posterior film. Superiorly, the peritoneal cavity is clearly delimited by the diaphragm. Inferiorly, the configuration of the peritoneal cavity is determined by the peritoneal reflections from the rectum, the uterus and the bladder and by the size and location of these structures. The lateral limits of the peritoneal cavity are frequently well delineated by the properitoneal fat line (Fig. 1). Superiorly, this properitoneal fat line becomes continuous with subdiaphragmatic fat and inferiorly with fat within the iliac fossa. When the properitoneal fatty layer in the iliac fossa is thick, the lateral extent or width of the peritoneal cavity may be relatively narrow as the true pelvis is approached (Figs. 2 & 3). When examining a radiograph of the abdomen, it is within these boundaries of the peritoneal cavity that one visualizes the various portions of the gastrointestinal tract. Moreover, the peritoneal cavity is not a simple continuous cavity but is rather effectively subdivided by the transverse colon and the transverse mesocolon into an upper and lower compartment. The stomach is attached to the transverse colon by the gastrocolic ligament and, in general, variations in the position of these structures parallel one another. Posteriorly, none of the small bowel can extend to a level higher than the attachment of the transverse mesocolon. Small bowel loops may extend anteriorly and become interposed between the liver and the abdominal wall or the diaphragm above the transverse colon. Interposition of loops of small bowel between the stomach and the liver, and the stomach and the abdominal wall or diaphragm is rare. It is also rare for loops of small bowel to extend anteriorly in front of the splenic flexure of the colon. The lesser peritoneal sac is a potential space but its existence explains the fact that none of the hollow viscera normally occupy a position behind the stomach and in front of the spine. Loops of bowel in this area therefore must represent an internal hernia through the foramen of Winslow. In a sense, the mesentery of the small bowel is another partition within the peritoneal

cavity but it presents no barrier to the movement of small bowel loops from one side of the abdomen to the other since the small bowel is attached along its free border. The length and width of the mesentery as well as its redundancy, however, must determine the limits of excursion of individual loops of small bowel. To some extent, the mesentery of the sigmoid acts as a barrier to small bowel loops entering the left side of the iliac fossa or the left side of the pelvis. The circumferential extent of attachment of the ascending and descending colon retroperitoneally is variable. Ordinarily, when loops of small bowel are seen to be located lateral to these portions of the colon, these loops are located in front. However, in many instances, there is a sufficiently long mesentery attached to these portions of the colon as well as to the hepatic and splenic flexures to permit loops of small bowel to extend more laterally behind these portions of the large bowel. In instances of interposition of the colon in front of and above the liver, the falciform ligament seems to play no role as a barrier and is presumably absent or poorly developed.

With perfect preparation of the patient, there theoretically should be no gas and little fluid in the gastrointestinal tract except for the bubble in the fundus of the stomach. Nevertheless, the collapsed stomach, small bowel and colon are filled with redundant mucosa and submucosa so that the overall caliber is considerably greater than might be anticipated. This redundancy of the layers within the muscularis propria is the result of a relative lack of elastic tissue as well as active contraction of the muscularis mucosa. In the absence of gas, it is difficult to recognize fluid-filled loops of bowel (Figs. 4 & 5). When markedly distended with fluid (Fig. 6), the increased density which follows the outline of the stomach, small bowel or colon can ordinarily be recognized without difficulty. Recognition of such fluid-filled areas is facilitated by contrast with adjacent fat which serves to delimit the filled region because of its relative lucency. From a radiographic point of view, it is useful to consider the abdominal cavity as filled with fat within which both the retroperitoneal as well as the intraperitoneal viscera are suspended or enclosed (Figs. 7-12). The radiographic density of the abdomen is considerably less than it would be if it were completely filled by tissue of water density. In other words, the abdomen is considerably more lucent than would be anticipated from its thickness and the density of the mid-portion of the abdomen is not greatly different from the flanks. Localized increase in density can occur therefore without any increase in diameter of the abdomen because of displacement of the fat which ordinarily occupies the region (Fig. 13). When an increase in antero-posterior diameter is due to fat as in obesity or with a large fatty tumor (Fig. 14), there is remarkably little increase in overall density. Such a large fatty tumor must be recognized by displacement of adjacent viscera. A small tumor composed of fat can be recognized only if it is well demarcated, for example, by a capsule of water density (Fig. 15). When an increase in antero-posterior diameter results from ascites or a large solid tumor or large collections of fluid in the gastro-intestinal tract, there will be a remarkable overall increased density which is added to the normal density of the abdomen. In a somewhat similar fashion, a "mass" on the abdominal wall which

projects outwards from the skin, for example, a colostomy, also shows an easily recognizable increase in density. A fold in the skin or a depressed scar may appear as a lucent line (Fig. 16) with an adjacent poorly defined area of increased density.

Normal fat within the peritoneal cavity includes the serosal fat covering the viscera which is relatively scanty except for the appendices epiploica of the colon. The bulk of the intraperitoneal fat is made up of fat within the greater omentum, the mesentery of the small bowel, the mesentery of the sigmoid and the other mesenteries, peritoneal attachments or "ligaments" between the various viscera, and between the viscera and the abdominal wall. These peritoneal folds include the gastrocolic ligament, the transverse mesocolon, the lesser omentum and the gastrosplenic ligament. The fat in these regions is continuous with the retroperitoneal and properitoneal fat. In some areas it is difficult to decide the exact location of a fatty density. This is true for example along the margins of the ascending and descending colon where the properitoneal and retroperitoneal fat fuse and become continuous at the peritoneal reflections. Hollow mobile viscera in contact with each other are practically always separated by a thin layer of fat. There is no fat line between the gall bladder and the liver. There is often considerable fat in the iliac fossae, in the lateral walls and in the floor of the pelvis, around the kidneys and adrenals, and in the subhepatic and subdiaphragmatic regions. Ordinarily, the only indication of the presence of these fatty collections or deposits is the visualization of adjacent viscera of water density. The normal fat in the abdominal cavity is quite homogeneous, that is, the interlobular connective tissue septa are rarely evident. When an area containing fat shows gross interlacing septa or soft tissue strands, this is indicative of neoplasm (Fig. 17), edema or inflammatory change (Fig. 18). It might be noted that the amount of abdominal fat and the development of the omentum is less in children and therefore the delineation of intraperitoneal viscera in this age group is more difficult.

Of greater importance from a radiographic point of view than the abdominal fat within the peritoneal cavity is the presence of gas within the lumen of the gastrointestinal tract. There is a considerable amount of experimental information as to the source of gas within the gastrointestinal tract but unfortunately much of this does not apply to the physiological state (5). Air enters the stomach normally during swallowing and no doubt some of this air enters the small bowel. Air introduced directly into the small bowel may reach the colon in about fifteen minutes. The average normal amount of gas in the gastrointestinal tract is said to be about 115 cubic centimeters (6). It has been said that 10 liters of gas are formed in the gastrointestinal tract daily but that ten to twenty times more gas is absorbed from the intestinal tract than leaves via the rectum (7). No collection of gas in the gastrointestinal tract can be considered to be fixed in composition unless equilibrium with the blood gases in terms of the individual partial pressures has been achieved. As a result, the composition of swallowed air is changed as it approaches equilibrium with capillary and venous blood (8). Most of the gas formed within the gastrointestinal tract consists of carbon

dioxide produced by interaction of gastric, pancreatic and small bowel secretions but this gas does not appear as gross collections within the small bowel since it remains in solution and is promptly absorbed into the blood. It would appear that under normal circumstances much of the gas which is seen in the colon and in some cases in the distal ileum is produced locally as a result of bacterial action. Fermentation of one gram of cellulose will produce more than 300 cubic centimeters of gas (7). In addition to carbon dioxide, methane and hydrogen are produced by bacterial action. Ammonia and hydrogen sulphide are produced in the colon as a result of bacterial action on protein residues. These "foreign" gases are not normally present in significant quantity in the tissues or the blood and are only slowly absorbed into the blood stream. Their local production within the lumen of the bowel therefore represents a relative vacuum in terms of the oxygen, nitrogen and carbon dioxide normally present within the tissues. These normal gases must therefore leave the tissues to enter the collection in an effort to establish equilibrium of the partial pressures. In other words, the foreign gases produced within the colon have a "priming" action which causes the normal gases to enter the bowel (5). With the exception of carbon dioxide, these gases move relatively slowly so that most of the dilution of foreign gases which occurs within a short period of time is due to the addition of carbon dioxide. It is unlikely that any gas collection in a contractile viscus such as the bowel can be in true or permanent equilibrium despite the fact that its composition may have become identical with the blood gases. This is due to the physical circumstance that the pressure within a gas collection in the lumen of the bowel is greater than atmospheric pressure by the increment contributed by contraction and tension in the wall of the viscus itself. Therefore, except for the "priming" mechanism, under normal circumstances no large volume of gas enters the gastrointestinal tract by diffusion from the tissues or blood. Under abnormal circumstances, however, for example, a closed loop obstruction, a large quantity of gas may enter the bowel from the blood.

The bulk of the gas seen in the colon in mechanical large bowel obstruction comes from the blood (9). During the course of an intravenous or retrograde pyelogram, gas often appears in the stomach, small bowel and colon quite promptly (10). This apparently is related to relaxation of the bowel which may occur during these procedures (11). It would appear therefore that active relaxation of the bowel wall is the mechanism which serves to suck gas from the blood into the lumen of the bowel. Moreover, if function is disturbed locally, gas may diffuse from the tissues into the bowel lumen. This has been demonstrated for example by the injection of ethyl alcohol into the mesentery of the small bowel (12). When this is done, a short segment of the adjacent bowel may distend with gas and peristaltic activity in the adjacent segments may disappear or decrease. The diffusion of gas into the lumen of the bowel need not be related to any change in blood flow. It has been demonstrated that occlusion of the mesenteric arteries with or without occlusion of the mesenteric veins will also result in a large amount of gas appearing in the lumen. Under these abnormal circumstances, the normal response of the bowel wall to an in-

crease in intraluminal pressure, that is, a disproportionate increase in the tension in the wall, is disturbed so that a small increase in intraluminal pressure produces excessive relaxation of the wall and equilibrium can only be approached by the entrance of gas into the lumen. This type of abnormal response of the bowel wall is the physiological mechanism underlying the appearance of a paralytic ileus whether diffuse or localized ("sentinel loop"). When a segment of bowel loses its contractility or cannot collapse because of the presence of a rigid lesion such as a carcinoma, fluid or gas or a combination of both must fill the involved segment. Since fluid is ordinarily absorbed, it is more likely that gas rather than fluid will persist in such a rigid area. Because of the non-contractile nature of the wall, for example, of a carcinoma, tension within the wall does not contribute to the pressure of the gas within the lumen of the involved segment and a true permanent equilibrium may be reached. Moreover, motor or peristaltic activity proximal to a non-contractile or rigid segment can create sufficient momentum to squirt fluid through the area which may nevertheless remain filled with gas. If a cul-de-sac such as a diverticulum occurs in the main course of the stream, fluid and gas are likely to persist within it. A large diverticulum cannot contract completely to expel its contents. Another type of cul-de-sac which will retain fluid and gas is a postoperative blind end in which normal peristaltic activity is in the incorrect direction to induce emptying.

The fact that gas often appears and persists in a diseased segment of bowel is of great importance in the roentgen diagnosis of intrinsic lesions of the gastrointestinal tract from simple films of the abdomen. A persistent local collection of gas indicates either local obstruction or local paresis if the area is dilated, or, if narrowed, local fixation or rigidity. It is surprising how often a neoplasm, for example, of the small bowel remains persistently evident by gas within the lumen of the tumor. Moreover, the immediately adjacent portions of the bowel on each side of the relatively rigid area may also retain gas as well.

The caliber of a particular segment of bowel containing gas or fluid or both will depend not only on the response of the bowel wall to changes in intraluminal pressure but also on the pressure with which the contents are introduced. It will depend also on the length of the segment undergoing filling as related to the volume of the contents being introduced (13). Segmental closures are produced by local contractions which occur regularly and periodically throughout the small and large bowel. Under physiological circumstances, the strength of such a local contraction is limited (14) and therefore the degree of distension which can be achieved proximal to such a contraction is also limited. In the presence of a mechanical obstruction, it is the forceful peristaltic activity proximal to the site of obstruction which creates excessive intraluminal pressure and excessive distension. Secretions and gas entering the lumen of the bowel in order to establish equilibrium may also produce marked increase in intraluminal pressure if mechanical obstruction is present. Normally it is rare to find any region of marked distension, discrete or diffuse, within the course of the gastrointestinal tract. Any large discrete collection of gas is therefore likely to be within a diverticulum or a blind end or to lie outside of the bowel (Figs. 19 & 20). The physio-

logical pressures are simply not great enough and the segmental contractions not powerful enough to produce or maintain marked distension of the intact bowel. If abnormally high pressures are available, and the bowel wall is intact, distension will be uniform within the limits fixed by unyielding anatomical structures. If the bowel wall is diseased, distension may occur with little or no increase or an actual diminution in intraluminal pressure and a "flabby" appearance is likely to result.

Intrinsic lesions of the gastrointestinal tract except for obstruction or cul-de-sac formation rarely produce local abnormal distension or dilatation of a discrete segment. Occasionally, an excavating or penetrating carcinoma or a lymphosarcoma may be associated with a local increase in caliber at the site of the tumor. Intrinsic disease of the bowel on an inflammatory basis or due to vascular or functional disturbances may produce local dilatation but these are in the nature of a paralytic ileus of segmental nature. Most of the lesions of clinical interest produce a diminution in caliber or at least local decreased distensibility. In other words, the bowel lumen is ordinarily narrowed as a result of intrinsic disease or does not distend to the normal degree in response to the physiological intraluminal pressure. At first sight, this would appear to be unfortunate if our purpose is to recognize these lesions on simple films of the abdomen since it might appear that the normal stomach or bowel could have any caliber from zero to an upper normal limit. The fact of the matter is that there is a lower limit to the caliber of the lumen during filling or emptying. The stomach or a segment of small or large bowel does not normally remain "slightly open." This arises from the fact that, as intraluminal pressure is decreased and the caliber diminishes, active contraction in the bowel wall must increase (Fig. 21). As the diameter diminishes, a critical point is reached at which prompt collapse to a completely empty state will occur. This may be referred to as the "critical closing diameter." In a similar fashion, when intraluminal pressure within a closed segment of bowels is increased, a point is reached at which the lumen will abruptly open to a diameter characteristic of the particular part of the bowel under study, that is, there is a "critical opening pressure" (15). As the pressure within such a segment is further increased, the caliber will slowly increase until a limit is reached at which perforation will occur. During distension, the tension in the wall increases at a rate disproportionate to the increase in the caliber of the bowel despite the fact that the muscle in the wall is undergoing relaxation. This type of incomplete or controlled or graded relaxation in response to increases in intraluminal pressure is a physiological phenomenon dependent on an intact neuromuscular apparatus and is designated as stress or receptive relaxation (16). A response of this character which is entirely different from the phenomena seen during distension of an inanimate elastic container, is essential if marked changes in caliber with small changes in intraluminal pressure are to be avoided. From the point of view of our present discussion, the important feature of this normal response is the conclusion that a segment with an uncharacteristically small or narrow lumen cannot occur normally unless it is a transient phase during filling or emptying. Diameters less than a "characteristic" diameter

are unstable. The radiologist is well acquainted with the characteristic caliber of the various portions of the gastro-intestinal tract from long experience with it under a variety of circumstances.

In any segment of the gastrointestinal tract which contains gas, there is usually some liquid or solid content as well. The pattern seen on a film of the abdomen will therefore depend not only on the quantity of gas but the amount and nature of the other content as well. Specific patterns as seen in the stomach, small bowel and colon are described under the separate sections devoted to these areas. Several principles of general application, however, will be noted here. If free exchange of fluid and gas is possible, the gas will rise to the highest portion of the viscus as the result of the action of gravity. The segment containing gas will also rise as far as adjacent viscera or attachments to adjacent structures will permit. However, if the viscus containing fluid and gas does not lie in a single plane but is bent or has a curved course, more than one fluid level may be present (Fig. 22). This will be due to the formation of a water-trap, if the viscus is curved downwards, or an air-trap if the viscus is curved upwards. Except in the stomach, free exchange of fluid and gas over a long segment is not present normally because of the characteristic segmentation or compartmentation in both the small and the large bowel. However, when continuous distension of a segment of considerable length is present as, for example, in obstruction or ileus, trapping of gas or fluid collections may play an important role in the distribution of these materials and therefore in the picture seen on roentgen examination. Within the limits of physiological pressures, not only may the fluid be considered to be incompressible, but the gas as well. No essential change in the volume of the gas within the gastrointestinal tract will occur with the relatively minor changes in pressure that occur either normally or in the presence of obstruction. Since the pressure within a continuous collection of gas is uniform, such a gas collection serves as a useful roentgenological tool for studying normal distensibility. It must be emphasized, however, that the apparent free exchange of fluid and gas under the influence of gravity requires simultaneous active adaptation of the wall of the viscus to the changes in pressure hydrostatically produced. The changes in caliber and configuration produced by changes in position are determined by the physiologic response to the hydrostatic effects.

When a considerable amount of both fluid and gas is present in the stomach or in a rather lengthy segment of small bowel, the gas appears as a continuous column floating on the fluid. The width of the gas column will depend on the height of the fluid relative to the total diameter of the segment. If the gas occupies one-half or more of the total diameter, the gas column will extend to the periphery of the region. With more fluid and less gas, the gas column becomes relatively narrow but continues to occupy the mid-portion of the segment since this is ordinarily its highest part. Moreover, with normal bowel content, the borders of the gas column will parallel the actual borders of the bowel whether these are straight or bent. With all degrees of filling, the border of the gas column is a faithful reproduction of the inner aspects of the wall since the normal fluid

content of the stomach and small bowel "wets" the mucosa very well. In other words, normal contents have a marked capillary attraction for normal mucosa. This attraction is greater than would exist if the contents were simply plain water or a barium-water mixture. This capillary attraction is another name for the surface tension effects which determine the configuration of collections of gas adjacent to fluid and bowel wall. A gas column floating on fluid in any extended segment not only outlines the bowel margin along its sides but also at each end. The ends of such a column may be determined by physiological or pathological closure or may result from the fact that the level of the filled segment has become more dependent and therefore completely filled with fluid. The fact that the end of a gas column is floating on fluid can often be recognized by a tapering configuration (Fig. 23) and the continuation of a broad, homogeneous density in the course of the bowel. The exact configuration under these circumstances will depend on the degree of acuteness of the angulation at the junction of the completely filled and partially filled segments as well as its exact direction.

If only small quantities of gas are present within a fluid-filled segment, they will appear as small floating bubbles which, in general, do not have a circular configuration but rather fill out the various crevices within the mucosal surface. To some degree, this is in contrast to bubbles or gas collections floating on a barium-water suspension which may have a shape independent of the adjacent bowel wall (Fig. 24). Numerous small bubbles are rarely seen immediately adjacent to each other since they ordinarily fuse to form a single continuous column of gas because of surface tension effects. A small collection of gas in the small bowel has a characteristic crenated or fluted appearance because of the numerous folds ordinarily present in this area (Fig. 25). If the lumen is wider and the collection of gas larger, the wall is smoother although residual valvulae conniventes remain evident. Occasionally a gas collection within the small bowel may show a rather bizarre configuration related to the marked twisting and turning of normal loops of small bowel or as a result of extrinsic pressure by adjacent loops. A small gas collection in the colon normally does not represent a bubble floating on fluid since the contents of the colon are relatively solid (in the absence of cathartics etc.). A bubble in the colon therefore completely fills a portion of a haustrum and shows a rather sharply demarcated unseptated margin (Fig. 26). Obviously mottled contents within which numerous small bubbles are caught are abnormal both in the stomach (Fig. 27) and in the small bowel. On the right side of the colon a mottled appearance of the contents is characteristic of the fecal material. A somewhat similar appearance may be produced by gas trapped in gauze or packing material (Fig. 28). Gas bubbles caught in tissue such as the wall of the bowel (Fig. 29) or in the retroperitoneal space usually have a discrete character and are separated from each other by soft tissue septa. Bubbles lying within the interstitial tissues may be circular in configuration. If the gas lies in a tissue plane (Fig. 30) or a blood vessel (Fig. 31), the gas will appear as a streak or a tubular shadow. Gas appearing as thin lucent streaks may also be occasionally seen in fissures within

biliary calculi (Fig. 32). A faintly lucent line or streak which represents serosal fat or fat within muscle planes can ordinarily be distinguished from a linear gas collection without difficulty because of its relatively lesser lucency. There is ordinarily no difficulty in recognizing gas within a viscus which is not part of the gastrointestinal tract such as the biliary tree or the gall bladder, the urinary bladder, pelvis or ureter (Fig. 33) or gas in the retroperitoneal space (Fig. 34). With the patient recumbent, gas free in the peritoneal cavity may be recognized by the fact that the outer borders of the colon and the small bowel are clearly delineated (Fig. 35). Occasionally, however, gas may be trapped within the peritoneal cavity, for example, by the falciform ligament (17) (Fig. 36) and create confusion in interpreting gas shadows.

From a physical point of view, the hollow viscera may be considered as elastic containers which are governed not only by anatomical and physiological specific characteristics but also by general physical laws (18, 19). For example, at any steady state, the law of Laplace (Fig. 37) must be fulfilled (15). This law states the relationship which must exist between the pressure within the container, the pressure outside the container, the diameter of the container and the tension in the wall. It is the difference between the pressure inside and the pressure outside, that is, the "transmural pressure", which is the force which serves to maintain distension. The change in pressure across the bounding surface, the wall of the bowel for example, depends not only on the tension in the wall but also on the shape of the surface. For a given tangential tension or hoop stress in the wall and a given diameter, the difference in pressure across the wall of a spherical container is twice that across a cylindrical container. This arises because of the double curvature of a sphere. The tension in a longitudinal direction in such a cylinder, however, would equal the tension in the wall of the sphere. Along the course of a uniformly distended segment of bowel, the longitudinal tension must be uniform unless there is a local point of fixation of either extrinsic or intrinsic origin. These points of fixation may be in the nature of struts produced by segmental contractions or anatomical features of a fixed nature. If the volume of a distended segment or viscus is not permitted to change and if the muscle in its wall were to relax spontaneously, the configuration would have to change in the direction of assuming a more spherical shape. If, however, the muscle should contract instead of relax, the configuration must approach a flatter or cylindrical configuration or the intraluminal pressure must rise. If the distended segment is spherical and fixed in shape, and if the muscle were to relax, the volume cannot remain constant but additional gas or fluid must enter. While these physical relationships may not be of great practical importance at present, they are noted because they are basic for the understanding of the configurations assumed by the various portions of the gastrointestinal tract. Under normal circumstances, intraluminal pressure does not differ a great deal throughout the gastrointestinal tract. Under resting conditions it measures between five and ten centimeters of water. Moreover, in the recumbent position, intraperitoneal, that is, extrinsic pressure on the hollow viscera, is not very different throughout the abdominal cavity amounting to about five centi-

meters of water (20). With the patient erect, intra-abdominal pressure is somewhat greater in the lower portion of the abdomen because of hydrostatic effects. However, since hydrostatic pressures are applied both internally and externally, they are not of great importance in determining the transmural or distending pressure. Other things being equal, therefore, the caliber of a particular loop of small bowel is independent of its position in the abdomen. It is of interest that the haustral pattern of the colon is a very suitable design to permit fine adjustments of configuration to changes in intraluminal pressure. The individual haustra can adapt their local curvatures to pressure changes without affecting the caliber of the central channel. Because of the variety of contents of this portion of the gastrointestinal tract and the large number of segmental contractions, such fine adjustments appear to be essential in this area.

Several other technical principles must be mentioned because they are of importance in the interpretation of simple films of the abdomen. A common effect seen in radiography is the appearance of a white border whenever a markedly lucent zone is present immediately adjacent to a dense area (Fig. 24). This border zone is thin, one or two millimeters in width, and forms the boundary between the lucent and dense regions. This zone is in the nature of a radiographic artefact and does not represent an anatomical structure. It has sometimes been explained on the basis that it represents an optical illusion but physical factors may also play a role. At any rate such a thin white border is often seen adjacent to a gas-filled viscus and should not be mistaken for the full thickness of the bowel wall. When a septum is seen traversing the gas column in the small bowel or colon, this of course is not an indication that it completely divides the lumen. In most such instances, the actual opening in the septum cannot be visualized. The fact that a septum is circumferential in nature is indicated by indentations on each profile at the same transverse level. Completely circumferential septa are ordinarily quite flat and plane. However, on a radiograph, they may appear to be curved or show an arcuate configuration. This indicates that the circumference has been projected and that the plane of the septum forms an angle with the x-ray beam. Since the septa are ordinarily perpendicular to the bowel wall itself, such a curved projection, for example, of haustral markings, indicates an oblique course of the bowel in relationship to the plane of the film. When adjacent septa in a segment over a relatively short distance change their projected configuration or overlap, this indicates that the bowel segment is tortuous. The large variety of septal projections seen in the course of the colon particularly on the right side is related to these projection phenomena and can be extraordinarily complicated because of the trifoliate nature of the haustral septa.



Fig. 1. The fat intervening between the muscular planes of the abdominal wall (arrow) is manifested by thin lucent lines. The fat lateral to the ascending colon is properitoneal fat reflected retroperitoneally.

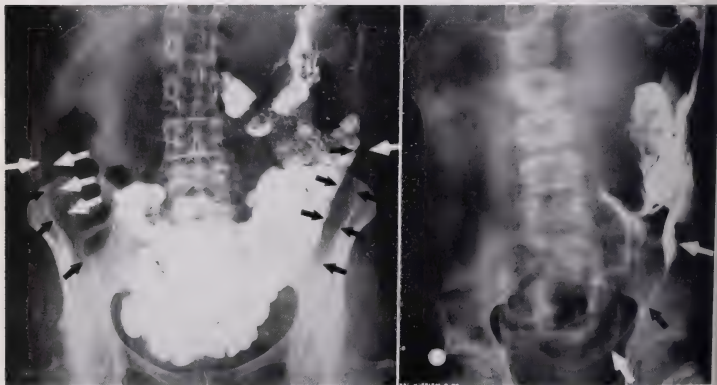


Fig. 2 (left). Prone. The lateral limits of the peritoneal cavity are frequently well seen by contrast within the fat in the iliac fossae (between arrows). The inferior extent of the peritoneal cavity is located at the periphery of the small bowel loops lying within the pelvis.

Fig. 3 (right). Aqueous contrast material entered the peritoneal cavity during splenoportography and outlines the lateral border of the peritoneal cavity (arrows). Note that the lateral half of the iliac fossa lies outside of the peritoneal cavity.

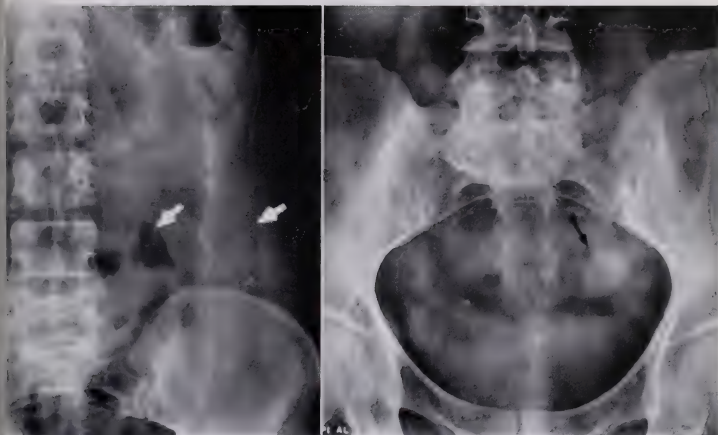


Fig. 4 (left). Fluid filled loops of small bowel make up the densities occupying the left lumbar gutter. A "loop", convexity inferiorly, is faintly evident (between arrows) above the iliac crest. The medial margin of this loop appears to flatten an adjacent gas collection in the small bowel (medial arrow). The lateral margin extends behind the colon to the abdominal wall. Note that the outer contours of the descending colon can be faintly traced over a considerable distance. The redundant mucosa in the collapsed empty colon (evacuation film after barium enema) contributes more than half of the overall density.

Fig. 5 (right). A loop of sigmoid (arrow) containing some fecal material is seen "on-end" and therefore appears unusually dense. The adjacent segments which lie parallel to the frontal plane are only faintly outlined.

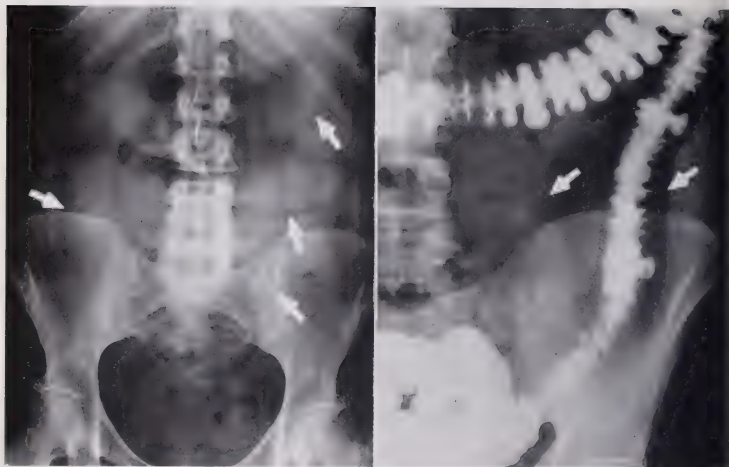


Fig. 6 (left). The upper abdomen is increased in density as a result of markedly distended loops of small bowel filled with fluid. The outer margins (arrows) of several wide loops are indicated by contrast with adjacent fat. An obstructing carcinoma of the small bowel was found at exploration.

Fig. 7 (right). The left lumbar gutter from the abdominal wall (lateral arrow) to the psoas margin (medial arrow) is lucent indicating the presence of considerable retroperitoneal fat. The barium-filled descending colon is enclosed by this fat.



Fig. 8. The wall of the descending colon and sigmoid is clearly delineated by gas in the lumen and (arrows) on the outside. Note the "characteristic" caliber of the gas-filled bowel.

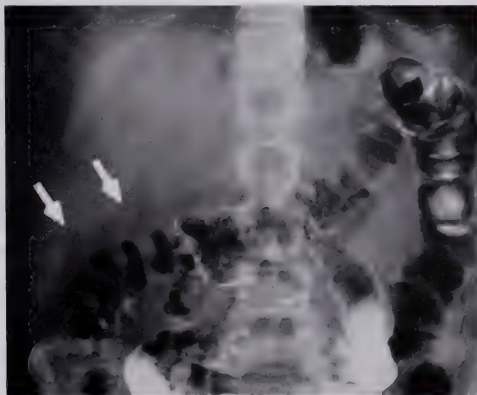


Fig. 9. The configuration of the inferior surface of the liver (arrows) is clearly indicated by subhepatic gas. (An ileo-transverse colostomy is present).



Fig. 10. The inferior and medial margins of the gall bladder (arrows on right) are delineated against adjacent fat. Peripelvic fat (arrows on left) within the kidney is demonstrated by lucent areas adjacent to the opacified pelves. The perirenal fat is large in amount particularly around the lower poles. Note that there is no fat line between the liver and gall bladder.



Fig. 11. A large amount of fat (arrows) is present between the spleen and the diaphragm. The diaphragm is clearly delineated by fat below and air above.

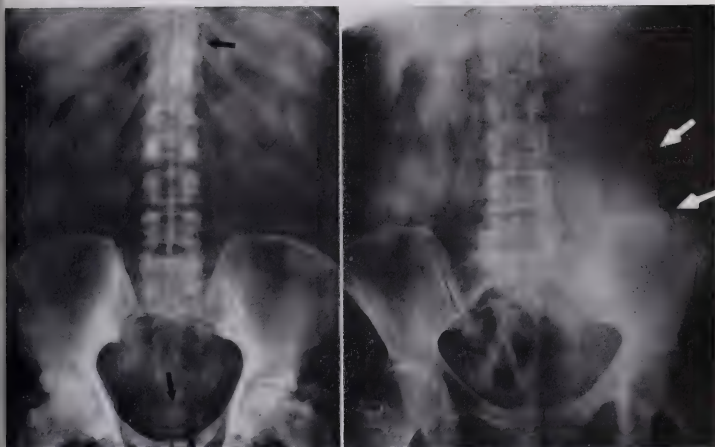


fig. 12 (left). Fat outlines the inferior and medial aspect of the left dome of the diaphragm (upper arrow). The outline of the bladder is completely delineated by surrounding fat (lower arrows). Throughout the abdomen, there are faint irregular lucent areas, most of which are due to fat. Note that the overall density of the mid-portion of the abdomen is not greatly different from the flanks despite its greater thickness. (Paget's disease is present in the pelvis).

fig. 13 (right). A retroperitoneal hematoma has replaced and displaced retroperitoneal fat (arrows) in the flank.

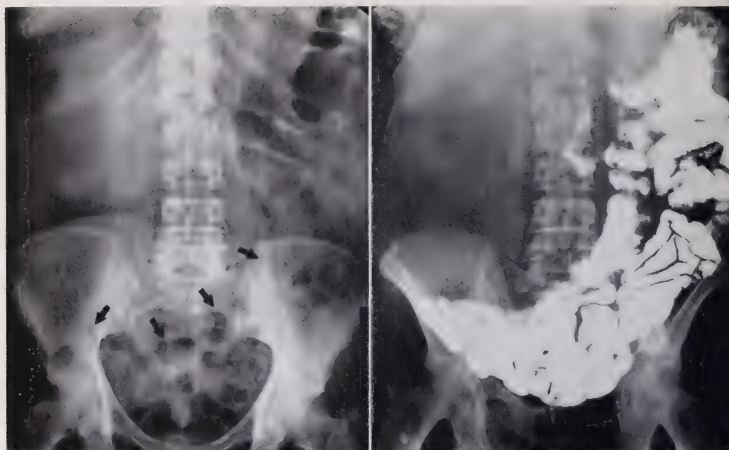


Fig. 14. Huge retroperitoneal lipoma.

Fig. 14A (left). The absence of gas shadows from the upper right abdomen is striking. The fact that the hepatic flexure and proximal transverse colon are markedly displaced (arrows) is not as obvious. There is no remarkable increase in density on the right side and the kidney and psoas margins are clearly evident. (Opaque material is present in the right buttock).

Fig. 14B (right). The marked displacement of the colon is clearly evident during barium filling. The huge mass is remarkably lucent.

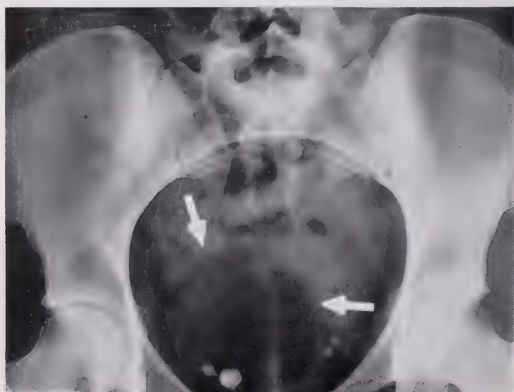


Fig. 15. A globular lucent shadow is seen in the pelvis surrounded by a thin capsule (arrows). Within its lower portion, there are calcific deposits which resemble abortive teeth. This appearance is characteristic of a dermoid cyst of the ovary.

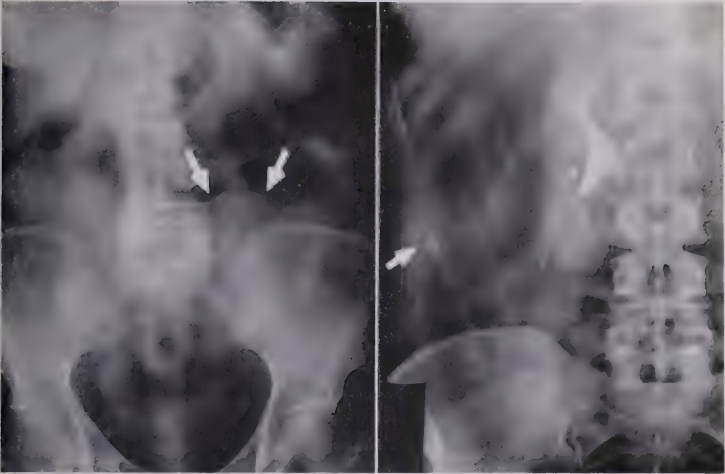


Fig. 16 (*left*). A sharp thin black line (arrows) which is too lucent for fat is seen above the crest of the ilium. An otherwise poorly demarcated dense area is present below this line. This was due to a depressed umbilical incisional scar with an adjacent bulge of the posterior abdominal wall.

Fig. 17 (*right*). Perirenal lipomyxosarcoma. The fatty mass in the right upper quadrant displaces and compresses the kidney. The lateral margin of the mass shows a capsule with a discrete nodule (arrow) projecting into the normal retroperitoneal fat. Note hazy irregular densities in the center of the fatty mass indicative of admixed tissue of water density. The normal fat lateral to and below the tumor is relatively homogeneous.

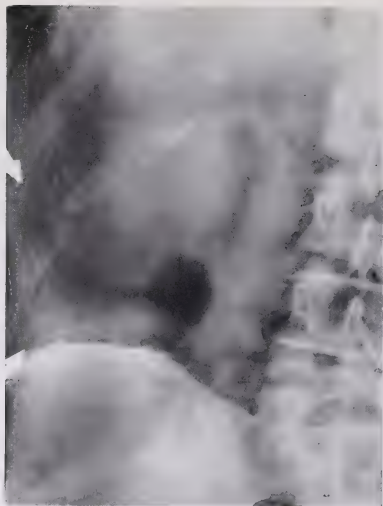


Fig. 18. Calculous pyonephrosis. The fat (arrows) lateral to and below the right kidney shows a increased opacity due to prominent interlacing strands of tissue of water density. At nephrectomy, there was a large amount of chronically inflamed fat around the kidney.



Fig. 19. A large globular collection of gas (arrow) is present in the pelvis. The margin is sharply demarcated without septa of any kind. A large diverticulum may have this appearance. In this case, there was an ovarian abscess communicating with the sigmoid as a result of diverticulitis.



Fig. 20. A large globular collection of gas (upper arrows) is present in the left lumbar region which is related to the colon. This was the result of retained gas and chronic infection in the kidney bed post-phrectomy. The dilated ureter containing opaque fluid (lower arrow) was left behind.

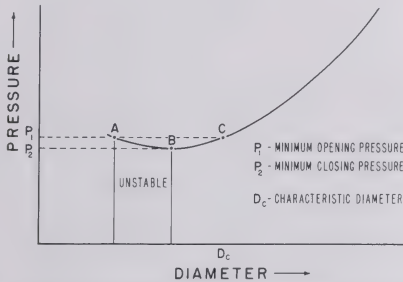
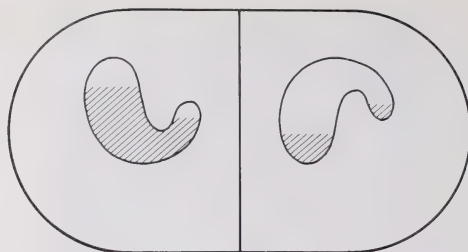


Fig. 21. Diagrammatic graphical representation of the relationship between distending pressure and diameters of a contractile hollow viscus. This is modeled from curves of urinary bladder pressures during filling and from "elastic diagrams" during distension of blood vessels (15). In the collapsed resting state A, the tension in the wall and intraluminal pressure are near minimum. Opening is resisted until a certain pressure (P_1) is reached. Filling then occurs very rapidly while the intraluminal pressure falls to minimum (B) and then rises to become equal to the pressure applied (C'). The diameter reached at this point may be designated as the "characteristic diameter" (D_c). If the pressure required to open the segment is exceeded, the diameter will increase further. During emptying of a filled segment, active contraction in the wall progressively reduces the diameter until a point is reached (B) at which prompt collapse to the empty state (A) occurs. The region between A and B in which pressure and diameter have an inverse relationship is unstable. The small difference in diameters at B and C' , i.e., between the characteristic closing and opening diameters, may be neglected for our present purpose. The intraluminal pressures created by normal motor activity correspond closely to the pressures required to open a contracted area.



WATER TRAP

GAS TRAP

Fig. 22. A viscus, such as the stomach or a long segment of bowel, filled with fluid and gas may show two fluid levels if sufficiently curved. If the curved portion is dependent, a "water-trap" may form. If the ends are dependent, a "gas-trap" may form.



Fig. 23. Supine. Subacute ulcerative colitis. The descending colon is filled in one continuous column with fluid proximally and gas distally. The lumbar gutter is more inferiorly located, i.e., more dependent with the patient supine, than the colon in the iliac fossa. The proximal end of the gas column shows a tapering configuration at its junction with the completely fluid-filled part (arrows).



Fig. 24. Prone. Barium enema. Large bubbles (arrows) are floating on the barium-water suspension in the transverse colon. The periphery of the bubble does not parallel the bowel wall exactly. While this is common with barium, it is unusual with normal bowel content since "wetting" of the mucosa is more marked. Note the thin markedly white line which forms the boundary between the gas bubbles and the barium. This does not represent any real structure and is in the nature of a radiographic artefact.

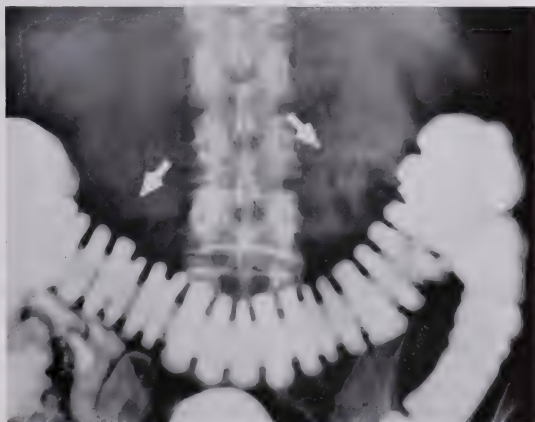


Fig. 25. Crenated and irregularly shaped bubbles or arcuate bubbly streaks (arrows) are characteristic of the appearance of small gas collections in fluid-filled loops of small bowel.

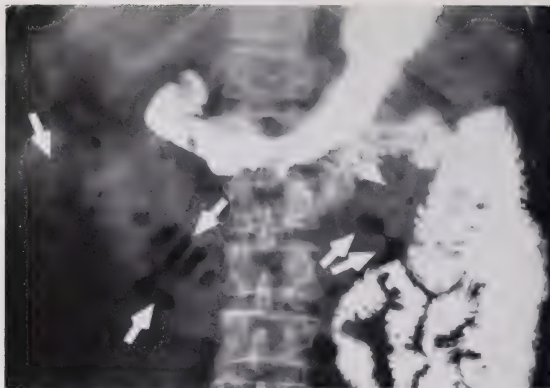


Fig. 26. Small collections of gas in the colon (arrows) occupy portions of haustra and are ordinarily not floating on fluid. Mottling in an otherwise dense area in the course of the colon (upper right arrow) indicates gas trapped in semi-solid fecal material.



Fig. 27. A mottled appearance of stomach contents (arrow) was caused by the introduction of a frothy mixture of nutrients prepared with an egg-beater via a feeding gastrostomy.

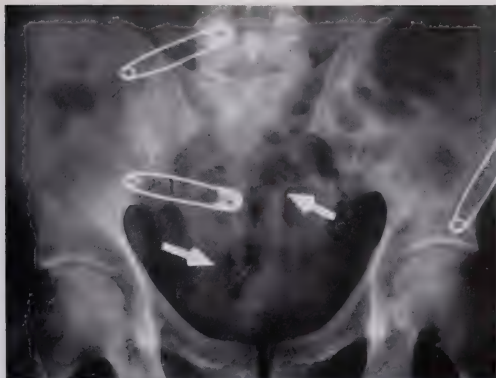


Fig. 28. Mottled shadows in the midline of the pelvis (arrows) are due to gauze packing after abdomino-rectal resection.



Fig. 29. Pneumatisis coli. A redundant sigmoid loop is distended with gas. The gas in the lumen is secured by gas in the wall which produces a markedly irregular outer contour (arrows) which in places shows discrete bubbles separated by thin soft tissue septa.

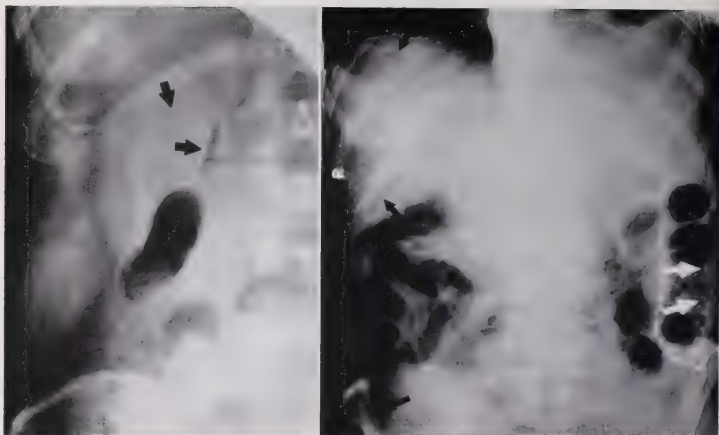


Fig. 30 (left). Streaks of gas (lower arrow) are present in the retroperitoneal tissues superiorly as result of a perforated appendix. There is also a tiny faint bubble (upper arrow) more laterally situated.

Fig. 31 (right). Innumerable bubbles in the wall of the bowel (arrows on left), gas streaks in retroperitoneal tissues, (lower right arrow) and gas outlining the portal veins (upper right arrow) within the liver shadow are present as the result of an overwhelming anaerobic infection.



Fig. 32. Gas-filled fissures (arrows) resembling bird tracks in the right upper quadrant are within non-opaque biliary calculi, not in the bowel.

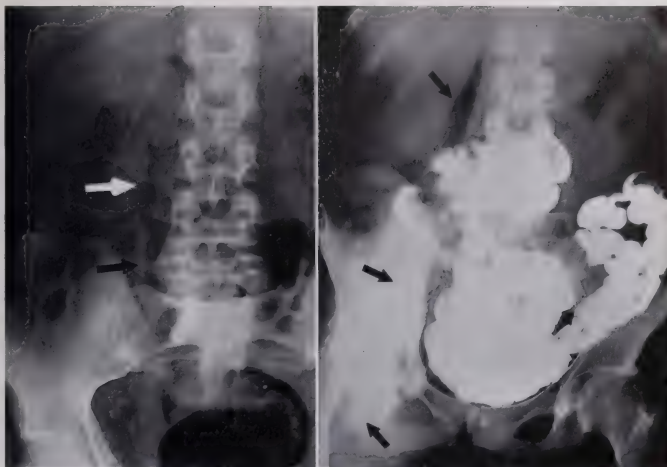


Fig. 33 (*left*). A gas-filled ureter (arrows) is evident after nephrectomy as a vertical band-like shadow adjacent to the spine.

Fig. 34 (*right*). A large triangular collection of gas (upper arrow) parallels the psoas muscle and is continuous with the barium-filled (lower arrows) lower portion of an iliopsoas abscess due to regional ileitis.

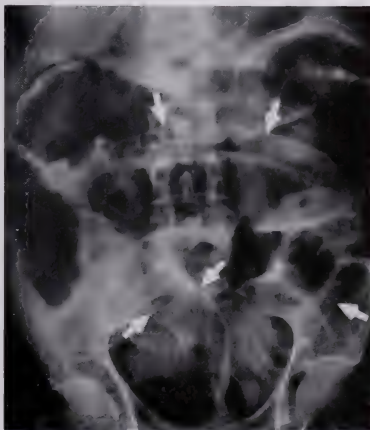
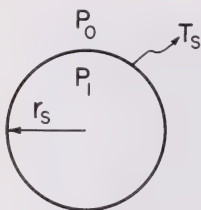


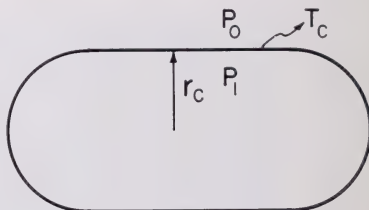
Fig. 35. Supine. Numerous loops of distended gas-filled small bowel occupy the mid- and lower abdomen. The outer contours of these loops are clearly delineated by gas in the peritoneal cavity. The wall of the bowel is therefore evident as a continuous white line (arrows) with gas on both sides. The right side of the abdomen is also distended with gas. Pneumoperitoneum was due to a cecal perforation two weeks after resection of the transverse colon for carcinoma.



Fig. 36. A broad vertical dense shadow (arrows) in the right upper quadrant is demonstrated by gas on each side. This is not a haustral septum in dilated colon but represents the falciform ligament outlined by intraperitoneal gas.



$$T_s = 1/2 (P_i - P_o) \cdot r_s$$



$$T_c = (P_i - P_o) \cdot r_c$$

Fig. 37. The law of Laplace.

Fig. 37A (left). The law of Laplace as applied to a sphere. T_s refers to the tangential tension in the wall; P_o is the pressure outside of or around the container; P_i is the pressure within the container; r_s is the radius. The tension is equal to one-half of the difference in pressure multiplied by the radius.

Fig. 37B (right). The law of Laplace as applied to a cylinder. T_c is the circular tension, i.e. the tension in the wall in a direction perpendicular to the long axis; r_c is the radius. The circular tension is equal to the difference in pressure multiplied by the radius. The longitudinal tension in the wall, i.e. in a direction parallel to the long axis, is equal to one-half of the circular tension.

CHAPTER TWO

The Stomach

I. THE NORMAL STOMACH*

Efforts to recognize intrinsic lesions of the stomach on films of the abdomen taken primarily for other purposes have no doubt frequently been made and to a considerable degree frustrated by the variety of appearances which may be seen normally. It is rather curious that the only type of examination in which this effort is made regularly is the routine film of the chest on which the gas bubble of the stomach is always carefully scrutinized. Filling defects within the gas bubble indicative of neoplasm have frequently been picked up in this fashion. The erect position in which the gas within the stomach rises and distends the fundus is well suited for this type of observation. Moreover, such patients are ordinarily not prepared by withholding food so that the gas bubble may be of considerable size. Attempts to study the distribution of gas and fluid in the stomach in the recumbent positions, both supine and prone, must be based on considerations of the physical and physiological principles which determine this distribution.

After several hours of fasting, the normal stomach is practically empty of fluid and contains a relatively small amount of gas. The *total* absence of gas from the stomach is highly suggestive of esophageal obstruction, particularly cardiospasm. The normally empty or contracted stomach is a rather small viscus with a fairly thick wall (Fig. 38). The wall is composed of the contracted muscularis propria, the serosa and the redundant mucosa and submucosa and projecting rugae. The ability to contract to a small size is an excellent indication of the absence of intrinsic disease. Almost all of the empty stomach lies to the left of the midline. Occasionally when the stomach is markedly transverse in position with little of the fundus projecting posteriorly, the distal extremity of the stomach may extend well to the right behind the liver (Fig. 39). Except in situs inversus (Fig. 40), there is ordinarily little difficulty in identifying the stomach because of its unique location and configuration. Marked cascading of the fundus of the stomach behind the body or an upward angulation of the body on the fundus (Fig. 39) may occasionally create some difficulty. Local variations in configuration are most commonly caused by extrinsic pressure of distended portions of adjacent colon. An indentation on the greater curvature aspect (Fig. 41) or the posterior wall of the stomach by a distended splenic flexure is quite common. It is more unusual for a distended hepatic flexure to cause extrinsic pressure on the antrum of the stomach (Fig. 42). The transverse colon when distended may cause a flattening and angulation of the greater curvature but more commonly produces a uniform upward displacement and a

* Figures for this section appear on page 139 et seq.

more transverse position of the stomach. It is rare for the transverse colon to occupy a position above the lesser curvature of the stomach. While the splenic flexure of the colon may lie behind the stomach, it never extends medial to the lesser curvature. However, loops of jejunum may extend behind the stomach further medially than the lesser curvature (Fig. 43) provided there is no marked distension of the stomach. Small bowel loops behind the stomach, however, never extend to the mid-line and are not seen normally above the distal or transverse portion of the stomach. The spleen is ordinarily located to the left and behind the body or fundus of the stomach but occasionally may be interposed between the fundus and the left leaf of the diaphragm. The medial border of the spleen may extend further towards the mid-line than the medial border of the stomach. It is rare to note interposition of small bowel or colon between the fundus and the dome of the diaphragm. Occasionally, however, the splenic flexure or distal transverse colon may lie in front of and above the level of the fundus of the stomach and, in the antero-posterior projection, simulate interposition.

Under most circumstances some fluid is ordinarily present in the stomach. Any large quantity of fluid is abnormal unless there has been recent ingestion. The amount of gas is also usually moderate in quantity unless there has been a recent meal. During the course of eating, a large quantity of air may be swallowed, much of which, however, is rather promptly eructated. The size of the gas bubble immediately after eating depends on the individual's eating habits, for example, the temperature of the food swallowed. If the food is hot, a considerable amount of air is ordinarily swallowed in an effort to protect the mucous membrane surfaces. Within a short time after eating, the gastric contents appear to be uniformly homogeneous without any mottling, trapped gas or gross lucent filling defects.

If the stomach were an inactive container of relatively fixed caliber, with change in the position of the patient, there would be simple exchange of fluid and gas under the influence of hydrostatic pressures, that is, gravity. This can occur physiologically, however, only when the stomach is markedly distended and parietic. Under ordinary circumstances, the stomach wall responds promptly to every local change in intra- or extra-luminal pressure. A readjustment of the tension in the wall of the stomach including graded muscular contraction or relaxation occurs with every such change in pressure (21). The response of the various portions of the stomach to a given pressure difference across the wall and the configuration which will result locally depends to some degree on the area in question. The fundus appears to be more easily distended than the remainder of the stomach and shows greater difficulty in completely collapsing or contracting. This feature of the fundus may be related to its unusual configuration which is effectively a broadnecked diverticulum. Because of this, complete collapse of the fundus requires infolding of its walls. In a rigid container, gas will always rise to the highest point. In general, this is also true of gas within the stomach. This occurs, however, not because the stomach is rigid but because only a small increase in intraluminal pressure is required to overcome

normal tonus and, once overcome, there is prompt distension to a characteristic caliber. When a collection of gas fails to rise to the highest portion of the stomach, in the absence of an intrinsic lesion which forms a barrier, it may be the result of abnormal extrinsic pressure over a localized segment or may be due to increased tonus of a localized area which fails to distend normally (Fig. 44). Localized increased tonus is often transient and may not be associated with intrinsic organic disease. With the patient lying on his back, the body of the stomach represents the highest part of this viscus and gas therefore rises to fill this area as a single collection (Fig. 45). Since the fundus is the most dependent portion with the patient in this position, any fluid in the stomach will ordinarily enter this region. If there is a large amount of fluid in the stomach, the antrum to the right of the spine may also be dependent and, with the patient supine, also filled with fluid (Fig. 46). With the patient on his back, it is therefore possible to have two collections of fluid, one in the fundus and one in the antrum, but any splitting of the gas column into two collections is abnormal. When a patient assumes the prone position, the gas rises to the fundus (Figs. 47 & 48) and fluid occupies the most dependent portion, that is, the body and antrum of the stomach (Fig. 49). Ordinarily, only a single gas collection is present in this, the prone, position since the antrum rarely lies sufficiently far posteriorly to trap any significant amount of gas. When the fundus does not extend markedly posteriorly and the stomach contains a considerable quantity of fluid, gas may be trapped in the body of the stomach to the left of the spine (Fig. 50). In such instances, this portion of the body of the stomach may be more posteriorly, that is, inferiorly, located than the fundus. It nevertheless is uncommon under normal circumstances to note more than one significant gas collection with the patient in either the prone or supine position.

Despite the fact that all the gas in the stomach ordinarily rises to the fundus when the patient is in the prone position, the intraluminal pressure within the fundus may not be sufficiently great to produce uniform distension of this relatively redundant region. A variety of rather bizarre configurations of the gas collection in the fundus (Figs. 51-53) may therefore be seen which creates confusion in the recognition of intrinsic abnormalities. These difficulties are exaggerated in those cases in which a considerable portion of the stomach lies in the sagittal plane, that is, front to back, underneath the left leaf of the diaphragm. In these instances, an end-on or axial view of a large part of the proximal portion of the stomach is obtained in the conventional antero-posterior or postero-anterior projection (Fig. 47). In the recumbent position, supine and prone, cascading of the stomach is often exaggerated. The correlation between the apparent location of a lesion on a simple film with the position observed on subsequent barium meal examination may therefore appear to be contradictory. In most instances, the lesion is located more distally in the stomach than would be anticipated from a simple film since the stomach elongates and straightens out as a result of distension during a barium meal.

In those patients in whom cascading is absent and in whom the fundus does not extend markedly posteriorly, the gas which collects in the fundus in the

prone position often has a somewhat triangular rather than globular configuration (Fig. 48). The distal margin of the gas collection may be somewhat pointed as it joins the contracted body of the stomach (Fig. 48). In other instances, the distal margin may be rather broad and the proximal margin more pointed (Fig. 54). A concentric pointed distal margin is the result of uniform circumferential contraction of the body of the stomach. A transverse distal margin indicates that the lumen of the contracted segment is more slit-like and compressed in the antero-posterior direction by adjacent viscera, the liver in front and pancreas or kidney behind.

When there is a large amount of gas in the stomach and relatively little fluid, a rather typical textbook picture of the stomach outlined by gas is frequently seen. With the patient supine, the gas column shows a curved, cylindrical configuration with parallel lesser and greater curvatures (Fig. 45). The wall of the stomach is convex outwards except in the region of the incisura or reentrant angle. Longitudinal rugae may be seen quite clearly projecting into the gas column (Figs. 40 & 46). The overlapping densities of the fluid-filled fundus, left kidney and the spleen can also be seen through the gas column. The overall caliber of the gas column is normally at least about 4 cm.; diameters intermediate between this characteristic caliber and the completely empty state are rare and indicative of spasm or extrinsic pressure (Fig. 55). No abrupt change in caliber is normally present. Since the stomach is ordinarily in the resting state, localized indentations of the contour as a result of peristaltic activity are not evident. Unless marked distension is present, the rugae along the contour of the stomach on both the lesser and greater curvatures cause a characteristic undulation or irregularity of the border which is typical of the gastric outline (Fig. 45). On the greater curvature aspect, rugae may appear as flat scalloping of the contour since they are predominantly transverse to the long axis of the stomach. On the lesser curvature, the sinuous course of the more vertical or longitudinal rugae produces a somewhat similar appearance. The boundary between the gas and the stomach wall is clearly delineated but it is also characteristic of the stomach that this boundary is frequently not exquisitely sharp or punched out but is slightly indistinct or fuzzy. The presence of normal rugae and a slight indistinctness of the inner aspect of the stomach wall are indicative of a normal mucous membrane surface. With the patient supine, the fundus is often clearly delineated as a globular homogeneous density made up by the wall of the stomach and the contained fluid. The lower curved wall of the fundus is ordinarily projected through the upper portion of the gas column within the body of the stomach (Fig. 45). The fluid-filled fundus may lie directly behind, to the left or to the right of the body of the stomach. The proximal margin of the gas column floating on top of the fluid often shows a tapering cylindrical configuration with a rounded end. The exact configuration of this margin of the gas column depends on the acuteness of the angulation between the posteriorly directed fluid-filled fundus and the anteriorly located body of the stomach. However, the proximal end of the gas column may be quite irregular and hazy because the gas column is thin as it approaches the fluid-filled fundus and gas extends irregularly for a variable distance proximally between rugae (Fig. 57).

The distal margin of the gas column, in the antero-posterior projection, is usually obscured by the spine. If the antrum extends to the right of the spine, the gas column may outline the pyloric ring (Fig. 44). More commonly, however, the pyloric ring is not seen in profile in the antero-posterior projection since the bulb ordinarily lies behind the antrum. Therefore the lateral margin of the antrum outlined by gas in the supine position corresponds to the greater curvature (Figs. 39 & 42).

When there is a large amount of fluid in the stomach and relatively little gas, no gas pattern outlining the stomach may be seen. Close observation may indicate that the overall density in the anticipated position of the stomach is increased and that portions of the outer wall of the stomach are evident. Usually, if the patient is supine, sufficient gas will be present to form a short narrow lucent column within the region of increased density (Figs. 56 & 57) or the gas column may be broken up into small collections or bubbles caught in the valleys between folds (Fig. 58). The gas column floating on top of the fluid within the stomach follows the typical curvilinear outline of the stomach and is centrally located. When the stomach contains a considerable amount of gas, it is possible to judge the thickness of the stomach wall by the distance between the gas in the stomach and the outer margin of the stomach as outlined by fat (Fig. 47). This adjacent fat rarely appears as a thin discrete lucent line unless there is an adjacent viscus in contact with the stomach. In such instances, the fat line intervening between the walls of the two viscera is ordinarily clearly evident (Fig. 42). However, an abrupt change in density can ordinarily be recognized for a considerable distance along the greater curvature (Figs. 55 & 56) and also around the fundus of the stomach. Despite the fact that there is fat present in the gastro-hepatic ligament along the lesser curvature of the stomach, the outer wall of the stomach at this site can rarely be identified. This may be due to the fact that this ligament lies in the frontal rather than in the sagittal plane so that no significant thickness of fat is projected in the direction of the x-ray beam in the antero-posterior view. In many instances in which the antrum is subhepatic in location, there is sufficient fat in the adjacent tissues to permit visualization of the outer wall of this region along both the greater and lesser curvatures (Fig. 46). When the outer wall of the stomach can be seen, it is quite sharply demarcated and parallel to the inner wall without any discontinuities or local external projections. The thickness of the wall of the stomach diminishes as the stomach becomes distended but it does not become extraordinarily thin until extreme distension is reached. It is often difficult, however, to be certain of the exact thickness of the stomach since the apparent thickness may be partly the result of fluid within the stomach rising to an unknown level and obscuring the inner surface. Moreover, particularly in the region of the fundus, there may be sufficient overlapping in an on-end view of the stomach lumen to exaggerate the apparent thickness. As the stomach becomes distended with gas, the valleys between the rugae widen and the rugae become less prominent and less numerous. As distension proceeds, the rugae do not decrease in width appreciably but rather in height until completely effaced.

Occasionally, a film of the abdomen is taken during the course of peristaltic

activity in the stomach and as a result localized indentations of the gas column which represent peristaltic waves are evident (Fig. 59). These ordinarily present no difficulty in identification since they are similar to those seen during a barium meal examination, that is, they are rather deep and short on the lesser curvature and broader and flatter on the opposite greater curvature. Rarely, deep circumferential contractions produce an appearance resembling colonic haustra (Fig. 60). The walls of the stomach adjacent to a peristaltic wave bulge outwards to a greater degree than the resting wall. This observation is of some diagnostic importance since it indicates normal pliability. Occasionally, a localized protrusion into the gas column which does not appear to be peristaltic in nature may be seen. These are ordinarily rather flat and must be differentiated from tumor masses causing filling defects. They are most common along the greater curvature of the body of the stomach (Figs. 61 & 62) although they may occasionally be seen elsewhere (Fig. 63). They apparently represent localized areas of diminished distensibility which ordinarily disappear with further filling, for example, during the course of a barium meal. If a normal rugal pattern can be observed over their surface, differentiation from a tumor can be made. In many instances, however, barium meal examination or another film demonstrating the transient nature of the pseudomass is necessary for further elucidation.

In this discussion of the appearance of the normal stomach, the fact has been assumed but not specifically stated that the pyloric ring is ordinarily a barrier to the free exchange of fluid and gas between the stomach and duodenum. Rarely, gas in the antrum and the duodenal bulb may be continuous through a short narrow pyloric ring but this is a transient phenomenon. A widely patulous pylorus is an abnormal finding. It is not uncommon for a small amount of gas to be trapped in the duodenal bulb and this gas may persist within the bulb despite change in position of the patient. The position of the duodenal bulb in relationship to the antrum of the stomach is quite variable. The bulb is ordinarily located behind the antrum but may be above or below, medial or lateral, to the antrum. The gas collection in the bulb may serve to demonstrate the characteristic configuration of the base of the bulb (Fig. 64) which will then serve to confirm the location of the gas. In rare instances, a rather exquisite star-shaped pattern of the pyloric ring (Fig. 65) is seen as a result of gas trapped between radiating folds.



Fig. 38. Prone. Residual barium outlines the rugal pattern of the collapsed, contracted stomach. A thick fat stripe (arrows) delineates the outer wall of the stomach along the entire greater curvature. The apparent thickness of the stomach wall is indicated by the soft tissue density intervening between the barium and the fat line. There may be unfilled rugae, however, along the greater curvature so that the true thickness is exaggerated.

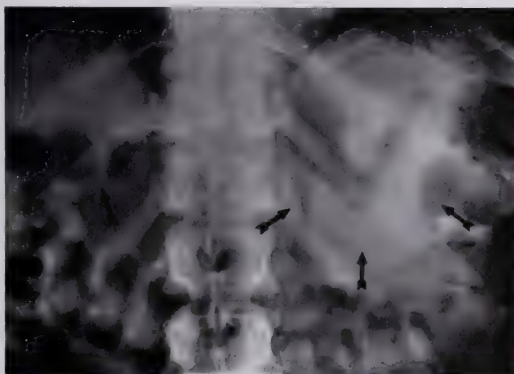


Fig. 39. Supine. Gas in the stomach is seen both to the right and to the left of the spine. It is likely that some gas is present in the mid-line as well but is obscured by the spine. The gas in the antrum shows an abrupt vertical boundary (arrow on right) as a result of extrinsic compression by a distended colonic caecum. The gas to the left of the spine has a V-shaped configuration which suggests the presence of a soft tissue defect in the fundus. However, the medial limb of the V represents the body of the stomach which is angulated upwards on the fundus. The outer wall of the stomach (arrows) is parallel to the gas column. The apparent great thickness of the stomach wall is due to fluid on which the gas is floating. The gas column shows scalloped margins corresponding to indentations by rugal folds.



Fig. 40. Supine. Preliminary film prior to oral cholecystography shows the stomach (arrows) high in the right upper quadrant without evidence of a liver shadow. The longitudinal rugae projecting into the gas column are clearly outlined. This was a case of situs inversus confined to the abdominal viscera and therefore unsuspected from the chest film.



Fig. 41. Supine. The stomach (and duodenal bulb) are distended with gas. The fundus extends unusually far to the left above the splenic flexure of the colon which indents the greater curvature. The soft tissue stripe intervening between gas in the stomach and gas in the colon represents the combined thicknesses of the gastric and colonic walls. A thin faint lucent fat line lies in the center of the gas stripe.



Fig. 42. The distended hepatic flexure produces an indentation on the greater curvature of the antrum. A thin faint fat line (arrow) intervenes between the gastric and colonic walls.

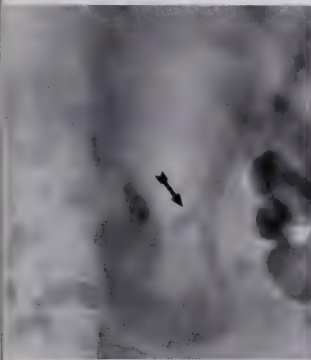


Fig. 43 (left). Supine. The stomach contains a considerable amount of fluid which proximally has a mottled appearance suggesting recent ingestion of food. A discrete ovoid gas collection (arrow) might be mistaken for a lesser curvature ulcer crater but actually lies in a loop of jejunum behind the stomach.

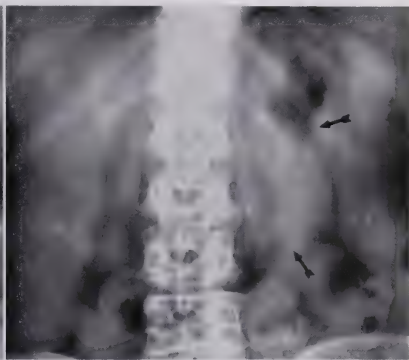


Fig. 44 (right). Supine. The gas column is split—one portion in the antrum and another part trapped in the fundus. This is the result of increased tone in the intervening segment (between the arrows) which is transient and unassociated with an intrinsic lesion. The pointed taper of the gas column at each end of the unfilled segment indicates abrupt concentric narrowing of the lumen. The soft tissue density between gas in the antrum and gas in the bulb is the pyloric ring.



Fig. 45. Supine. The stomach contains a considerable amount of gas and fluid. The dependent fundus is filled with fluid and is sharply outlined below and laterally (arrows) by adjacent fat. The gas column has a curved cylindrical configuration with clear but not punched-out borders. These borders are undulating and in places double as a result of superimposed sinuous rugae. The proximal portion of the gas column tapers slightly and ends in a blunt curve. The distal margin of the gas column is obscured by the spine.

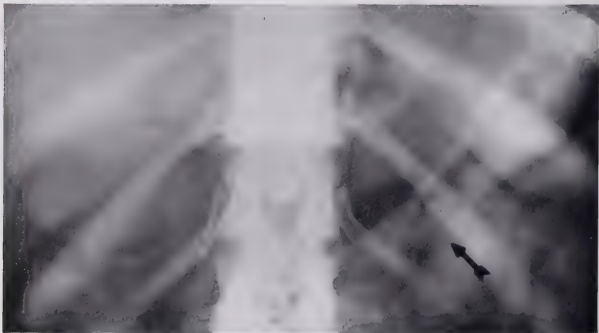


Fig. 46. Supine. The egg-shaped fluid filled antrum to the right of the spine is well outlined by adjacent fat. The outer wall of the greater curvature (arrow) is also clearly evident. A long longitudinal rugal fold projects into the gas column of the body of the stomach. Adjacent rugae along the greater curvature produce a scalloped appearance because of their transverse course.



Fig. 47. Prone. The gas is collected in the fundus which shows prominent rugae superiorly and laterally. The medial and inferior margins of the gas collection are duplicated, i.e. show a double density, indicating that the gas collection is not spherical but cylindrical. A considerable portion of the proximal part of the stomach overlaps the fundus and is seen on-end. The outer wall of the fundus (arrow) is clearly delineated and can be followed distally for some distance along the greater curvature of the fluid-filled body. Incidentally, the colonic wall is also faintly seen as a uniform soft tissue density surrounding residual barium in the lumen. A broad fat stripe (gastro-colic ligament) intervenes between the gastric and colonic walls. A paravertebral mass adjacent to D9 and D10 can also be seen.)

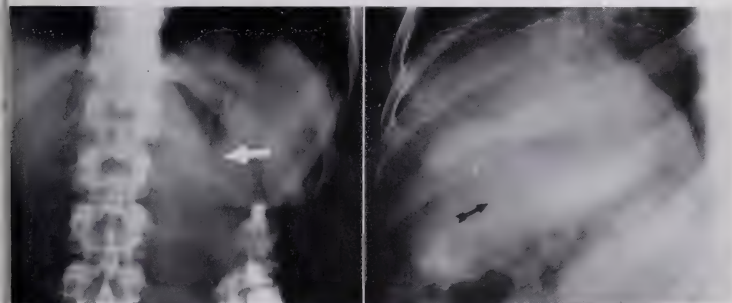


Fig. 48 (left). Prone. Little fluid and only a small amount of gas is present in the stomach. The fundus is not uniformly distended but shows a somewhat triangular configuration, apex directed distally. A narrow concentric column of gas (arrow) extends a short distance distally between rugae.

Fig. 49 (right). Prone, right side elevated slightly. Film taken during oral cholecystography shows the C-shaped, fluid filled antrum (arrow) below and medial to the opacified gall bladder. Gas in the stomach is confined to the fundus (not included on the reproduction).

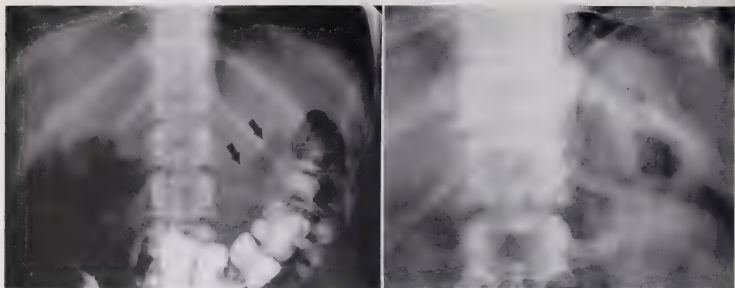


Fig. 50 (left). Prone. The gas fails to fill the fundus and remains in the body of the stomach to the level of the spine (arrows). This is unusual and presumably due to the fact that, in this case, this portion of the body of the stomach extended further posteriorly than the fundus.

Fig. 51 (right). Prone. The lateral wall of the fundus fails to distend symmetrically. The outer margin of the wall also shows an indentation at the same level.

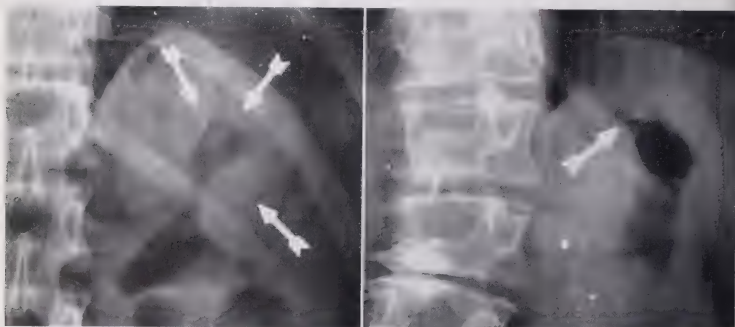


Fig. 52 (left). Prone. There is a bizarre configuration of the gas column in the fundus and proximal body due to multiple areas (arrows) of limited distensibility. No intrinsic lesion was present.

Fig. 53 (right). Prone. Another example of incomplete distension of the fundus probably related to compression by the liver associated with scoliosis of the spine. The beak-shaped prolongation towards the hiatus may be seen with a direct or sliding hiatal hernia. On barium meal examination, a small hernia was found; no intrinsic abnormality was present. The abrupt transverse distal margin of the gas column is presumably related to extrinsic pressure as in Fig. 54.

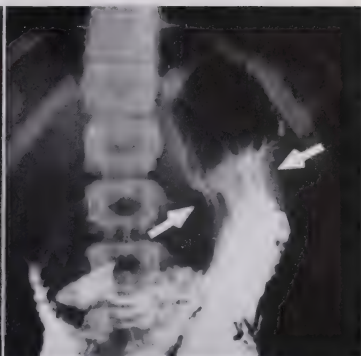


Fig. 54A (left). Prone. Residual barium occupies the distal part of the stomach and is separated from the gas in the fundus by a broad soft tissue density (between arrows). The gas in the fundus has a somewhat triangular configuration, base located distally.

Fig. 54B (right). Prone. Film taken during barium meal, prior to Fig. 54A with more barium in the stomach shows extrinsic compression from front to back of the segment immediately below the fundus (between arrows). This is presumably due to pressure by the pancreas in back and the liver in front. As a result, closure of the stomach in this area may be slit-like rather than circular or concentric.

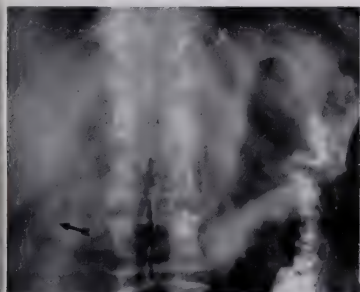


Fig. 55 (left). Supine. The gas column in the distal half of the stomach appears diffusely narrowed as if by a scirrhus carcinoma. The narrowing, however, is at the expense of the lesser curvature only. This appearance is the result of extrinsic pressure by the liver. Incidentally, the arcuate base of the bulb (crow) is clearly outlined by gas in the duodenum.

Fig. 56 (right). Supine. A narrow column of gas is floating on a large quantity of fluid. The soft tissue density between the gas and the outer wall of the stomach (arrows) is composed of gastric wall plus fluid. The gas column follows the curvature of the stomach and is lost between rugae proximally. The scalloped margins of the gas column indicate a normal rugal pattern.



Fig. 57. Supine. The stomach is almost completely filled with a considerable quantity of fluid. A narrow short gas column of irregular caliber (upper arrow) overlies the central part of the fluid. In this case the outer wall of the greater curvature is well delineated (lower arrow). If this were not so, the slight homogeneous increase in density of the fluid-filled stomach might be difficult to recognize.

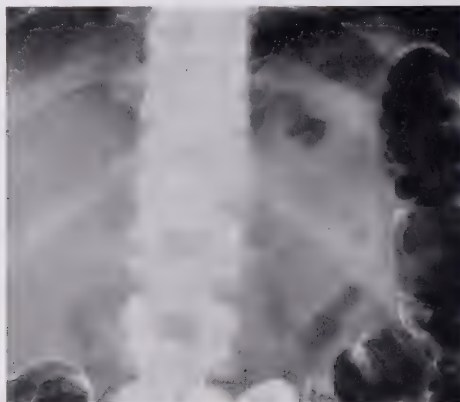


Fig. 58. Prone. The stomach contains a large quantity of fluid. The small amount of gas present is trapped in multiple collections between rugae and at each end of the stomach. These collections follow the curved configuration of the stomach and show scalloped contours corresponding to segments of rugae.

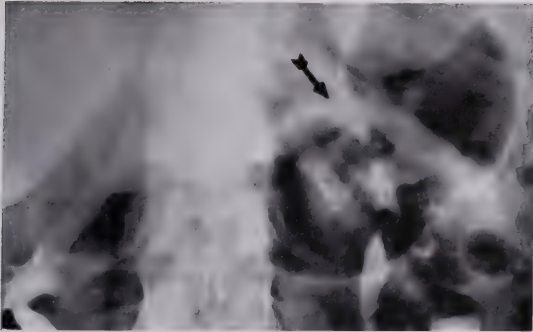


Fig. 59. Supine. The stomach is distended with gas on a film taken during intravenous pyelography. At the re-entrant angle, there is a deep indentation (arrow) characteristic of a peristaltic wave. Opposite this, on the greater curvature, a corresponding shallow indentation is present. The wall of the stomach adjacent to the peristaltic indentations bulges outward. As a result of marked gaseous distension, the rugal pattern is effaced and the inner wall of the stomach is sharply delineated. A thin dense white line parallels the border of the gas column in places. This is a contrast or border effect and does not represent the full thickness of the gastric wall. The spherical soft tissue shadow overlapping the proximal part of the stomach is the fluid-filled fundus.



Fig. 60 (left). Prone. The stomach shows unusually deep and circumferential peristaltic contractions (arrows).

Fig. 61 (right). Supine. The gas column shows a flat indentation (arrow) on its greater curvature which does not have the appearance of a peristaltic wave. This defect was not present on barium meal examination.

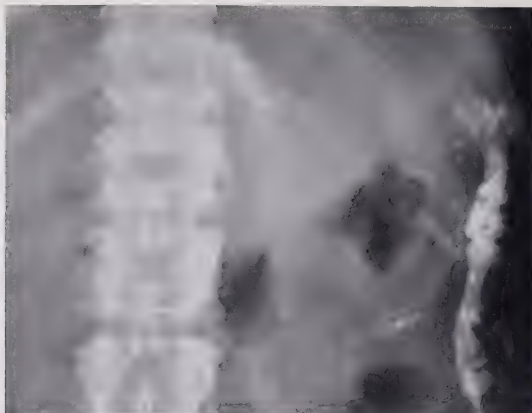


Fig. 62. Supine. A hemispherical protrusion into the gas column from the greater curvature suggests an intramural mass. Rugal folds can be recognized over the proximal surface of the defect. The residual barium in the adjacent transverse colon appears slightly displaced towards the defect. On barium meal examination, this defect was also noted but was variable in size and shape. The mucosa was intact. The patient had no gastric symptoms. The nature of this defect is not clear but apparently is extrinsic in origin and of no current clinical significance.



Fig. 63. Supine. A localized small soft tissue defect or indentation (arrow) is present high on the lesser curvature. This is presumed to be extrinsic in origin (splenic vessels?). The rugal pattern along the curvatures and within the gas column is well seen.



Fig. 64. Supine. Deep peristaltic waves subdivide the distal portion of the stomach. Gas trapped in the duodenum outlines the typical configuration of the base of the bulb with arcuate borders and a central dimple (arrow on right). The apex of the bulb is directed medially. A double contour (arrow on left) along the greater curvature is due to a parallel rugal fold.



Fig. 65. Prone. Gas trapped in folds radiating to the pylorus produces a "star-shaped" configuration within the antrum (arrow).

II. GASTRIC NEOPLASMS*

The roentgen findings on simple films of the abdomen indicative of a gastric neoplasm are identical to those seen during the course of a barium meal examination, as modified by considerations of the factors determining the distribution of gas and fluid in the stomach and by the variable degree of gastric distension. The *negative* contrast of the gas is utilized in the same manner as the *positive* contrast of barium. If little gas is present or if the position of the patient during the taking of the film does not permit gas to enter the involved part of the stomach, the lesion will not be evident. However, because of the lack of contractility associated with malignant neoplasms, there is often considerable gas in the stomach in such patients. Moreover, deep ulcerations will often retain gas independently of the position of the patient. The fact that the stomach is not completely distended in most instances is often not a drawback since a lesion of given size is more likely to be evident at least partly in profile.

A localized narrowing of the gas column when discrete and sharply demarcated is an unequivocal finding indicative of a rigid lesion, specifically, a scirrhus type of carcinoma. (Figs. 66 & 67). The narrowed gas column often is of irregular caliber with side walls which are flat or bulge towards the lumen. The proximal and distal margins of the involved area may show soft tissue excrescences or overhanging edges characteristically projecting into the gas. In films of good quality, the outer margin of the stomach may be seen to be abruptly interrupted at the site of the neoplasm or to bulge outwards or to produce a localized marked thickening of the wall (22). The normal rugal pattern along the contours of the involved segment is lost or replaced by a grossly irregular margin or bulky soft tissue protrusions. The boundary of the gas column may be quite hazy and indistinct or multiple contours may be seen on each side (Fig. 68). When a scirrhus carcinoma involves the entire stomach producing the picture of a linitis plastica, a rigid banana-shaped, narrow column of gas may be seen traversing the upper abdomen (Fig. 69). This appearance will persist despite changes in the position of the patient. When the scirrhus nature of the tumor is not as marked, the narrowed segment may be less obvious but the irregularity of the contours, the absence of a normal rugal pattern and the abrupt transition to normally distensible adjacent stomach may be evident. When the neoplasm is confined to one wall and involves a relatively small area (Fig. 70), a rather flat filling defect with abrupt demarcation from adjacent normal stomach and an irregular polypoid surface may be seen.

In contrast to those neoplasms of the stomach which appear as narrowed segments, the most obvious finding in another group of cases is a filling defect of discrete nature which protrudes into the lumen of the stomach (Fig. 71). These lesions are exophytic or polypoid in type and, when large, may completely occupy the lumen of the stomach (Fig. 72). In such instances, the fact that a large mass is present within the stomach may be overlooked. However,

* Figures for this section appear on page 152 et seq.

an interruption or a splitting of the gas column (Fig. 73) or collections of gas trapped in a bizarre configuration within a dense area (Figs. 74 & 75) often furnish clues to the correct diagnosis. Any collection of gas which appears to defy gravity and fails to rise to the highest possible point deserves special attention in an effort to determine the nature of the barrier. When a poorly demarcated soft tissue density is present along the anticipated course of the stomach, close examination may show faint lucencies within it which indicate an ulcerated or irregularly shaped surface. In some instances, an apparently sharply demarcated filling defect in profile may be demonstrated to be continuous with adjacent soft tissue protrusions into the gas column by examining the film under a bright light (Fig. 76A). Such a small profile defect may represent the elevated edge of a flat ulcerated carcinoma (Fig. 76B). In other cases, an irregular ulceration which traps gas is the obvious feature (Fig. 77). The ulceration seen in these instances is ordinarily quite large with multiple nodular projections into it. The fact that it is associated with a mass lesion is indicated by its location within a homogeneous soft tissue density. The ulcerated area may assume the "meniscus" configuration characteristic of the Carman sign (Fig. 77). Occasionally, the presence of a malignant neoplasm may be manifested by a peculiar conglomeration of gas shadows which cannot be individually analyzed but portions of which may show characteristic convexities towards the lumen (Fig. 78) or irregular filling defects.

The findings in lymphosarcoma or Hodgkin's disease of the stomach (Figs. 79 & 80) are essentially similar to those described in carcinoma with the exception that marked narrowing is absent. An appearance simulating a scirrhus carcinoma may be produced by a large intramural mass causing marked thickening of the wall in eccentric fashion (Fig. 80A). Central excavation within the tumor may retain gas and simulate a giant ulcer (Fig. 80B). Thick folds infiltrated by lymphosarcoma in a diffuse fashion may also be evident on a simple film (Fig. 81).

Small benign polyps of the stomach are not likely to be recognized on simple films of the abdomen. However, intramural tumors such as myomas may be manifested as sharply circumscribed filling defects with a smooth surface contrasted against gas in the stomach lumen. A punched-out aspect characteristic of a benign lesion is produced as a result of effacement of the rugal pattern over it (Figs. 82-84). The irregularity, rigidity or extensive ulceration of a malignant neoplasm is absent. There may, however, be well circumscribed deep central ulcerations manifested by small gas pockets or by the retention of previously administered barium or opaque material (Fig. 83). Although the tumor may not be well outlined in a particular projection, the fact that a mass is present may be suggested because of splitting of the gas column (Fig. 84). Benign tumors of the stomach are likely to be more difficult to discover on simple films of the abdomen than carcinomata because of the lack of rigidity and the absence of functional disturbances.

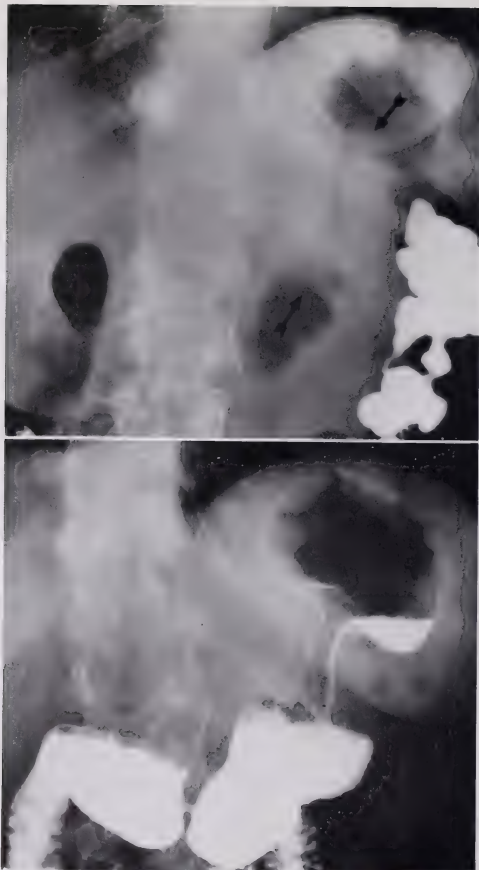


Fig. 66. Scirrhou carcinoma.

Fig. 66A (*above*). Prone. The body of the stomach presents a markedly narrowed discrete segment with irregular flat contours. Overhanging edges (arrows) are evident through the gas column both proximally and distally. Gas remains in the stomach distal to the lesion indicating that all of the stomach to the left of the spine lies in the same frontal plane. Close observation shows a normal fat line along the outer contour of the greater curvature distally which is abruptly lost at the margin of the lesion. This finding suggests serosal involvement.

Fig. 66B (*below*). Barium meal examination shows identical findings, typical of a scirrhou carcinoma.



Fig. 67. Carcinoma.

Fig. 67A. Prone. The stomach below the fundus is narrowed both on the lesser and greater curvatures. The narrowing begins abruptly with protrusion into the lumen from both sides ("hatchet-shaped"). In addition, faint soft tissue densities are evident through the gas column at the site of narrowing. The normal angulation of the body on the fundus is absent and mottled fluid contents may be traced distally.

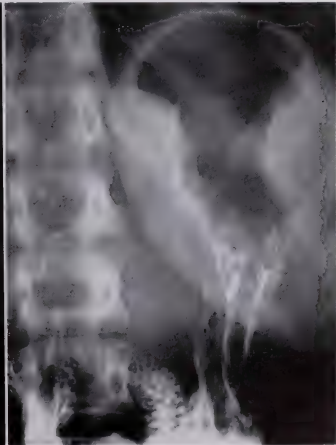
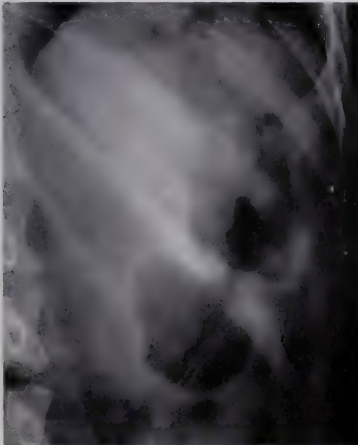


Fig. 67B (left). Supine. An unusual amount of gas remains in the fundus and the narrow, rigid appearance of this area is duplicated. Distally, active peristaltic contractions are present.

Fig. 67C (right). Erect. Barium meal examination shows classical findings of a thick scirrhous carcinoma.

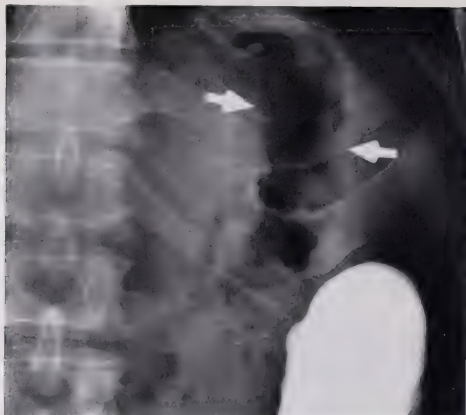


Fig. 68. Prone. Extensive carcinoma of the fundus and body of the stomach. The gas column is irregularly narrowed (arrows) with multiple soft tissue protrusions which are thicker and more irregular than normal rugae. The distal extent of the lesion is obscured by fluid and bubbles in the dependent portion of the stomach.

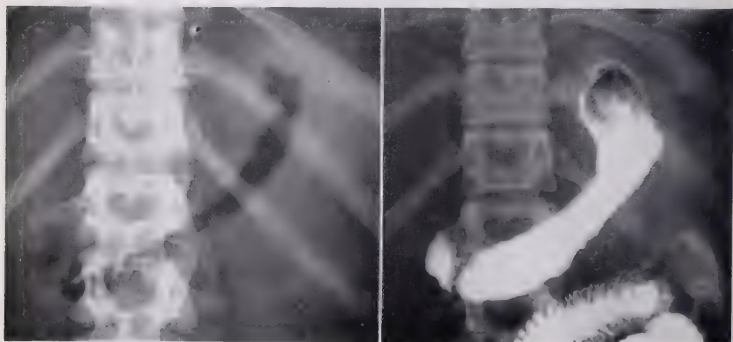


Fig. 69. Extensive scirrhus carcinoma.

Fig. 69A (left). Supine. A narrow column of gas outlines the entire stomach. The borders of the gas column are indistinct without any rugal pattern. A thick homogeneous density surrounds the gas column on both sides although there is no sharp demarcation of the outer wall of the stomach.

Fig. 69B (right). Barium meal examination shows identical findings.

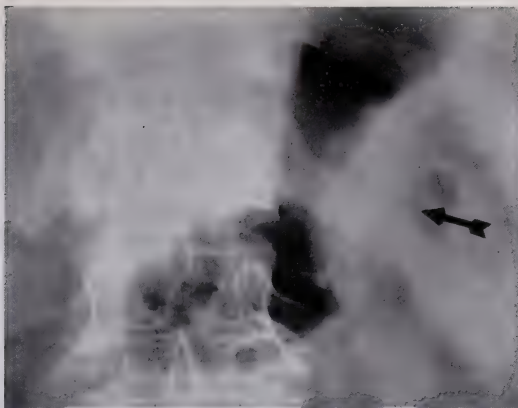


Fig. 70. Supine. Carcinoma. A broad-based filling defect is seen extending into the gas column from the greater curvature. The surface of this defect is irregularly nodular. The faint serosal fat line (arrow) is not displaced towards the lumen.

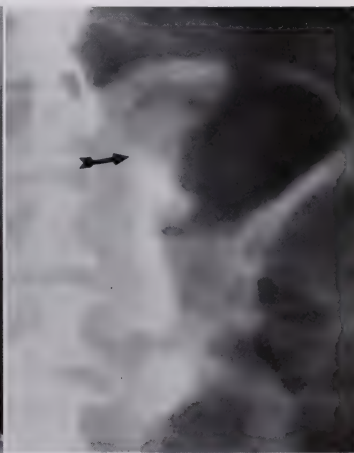


Fig. 71. Carcinoma.

Fig. 71A (left). Erect film of the chest. Convex or nodular protrusions into the gas bubble in the region of the cardia are classical findings.

Fig. 71B (right). Prone. The full extent of the lesion (arrow) is evident as a broad-based polypoid mass.



Fig. 72. Supine. Colloid carcinoma. The gas column is split because of a large defect (arrow) occupying and distending the body of the stomach. The gas trapped in the fundus outlines the knobby proximal margin of the tumor mass.

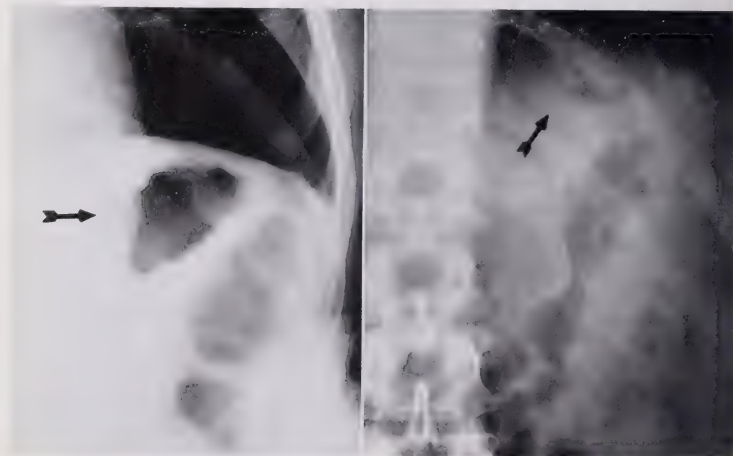


Fig. 73. Carcinoma of the cardia.

Fig. 73A (left). Classical findings on the chest film indicate carcinoma (arrow) of the cardia.

Fig. 73B (right). Supine. The large defect is obscured by fluid in the fundus. The small crenated gas collection (arrow) in the fundus, separated from the main gas column, is abnormal but difficult to interpret. Masses in this region are seen best with the patient erect or prone.

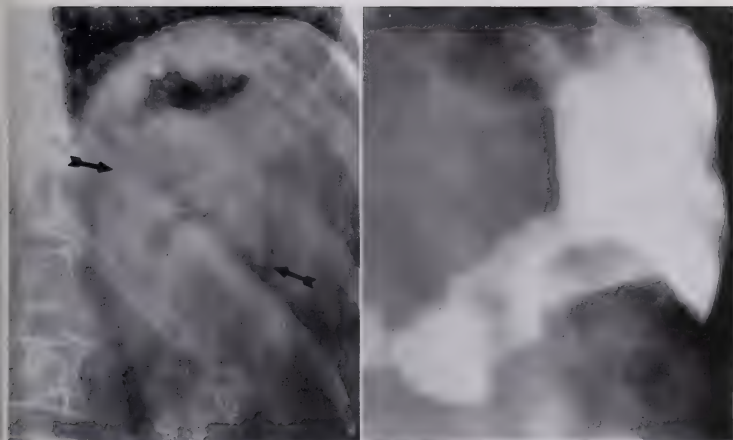


Fig. 74. Carcinoma.

Fig. 74A (*left*). Prone. A small amount of gas is present in the fundus with a broad density (between arrows) occupying the body and displacing the greater curvature fat line laterally. Within the density, several isolated collections of gas are present which do not follow the ordinary course of the gastric lumen or of gastric rugae.

Fig. 74B (*right*). Barium meal examination demonstrates a large irregular filling defect involving the entire circumference of the distal portion of the body of the stomach. The more proximal location of the lesion suspected from Fig. 74A is a common phenomenon attributable to the fact that the proximal normal portion of the stomach is contracted on the simple film.

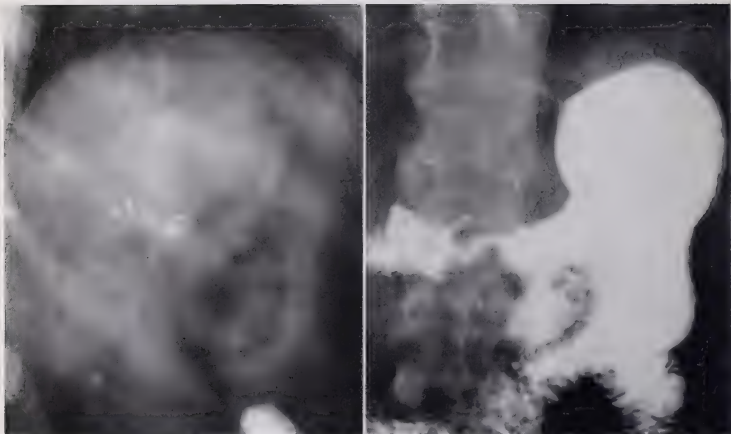


Fig. 75. Carcinoma.

Fig. 75A (*left*). Supine. Most of the gas in the stomach appears to be trapped in a long pocket along the greater curvature. Medial and distal to this region, several small isolated gas collections are evident which must be presumed to lie within a large neoplasm. (Ring-shaped calcifications are in splenic vessels.)

Fig. 75B (*right*). Barium meal examination shows a huge ulcerated carcinoma occupying the distal portion of the stomach and extending proximally for a considerable distance along the lesser curvature. The gas column seen on the simple supine film occupies the lateral uninvolved portion of the body of the stomach.

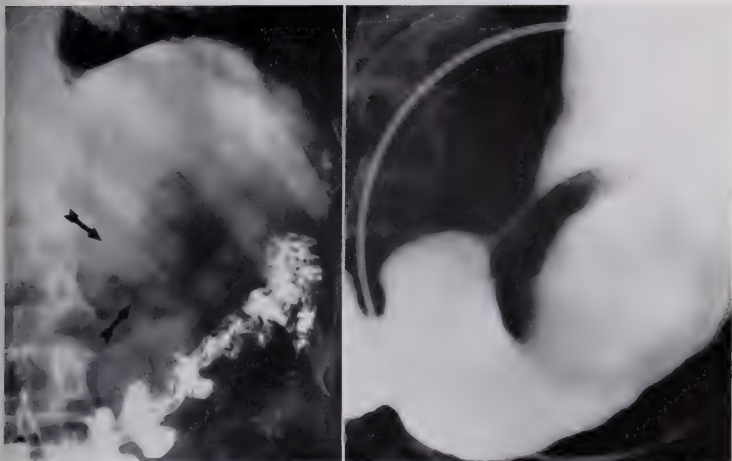


Fig. 76. "Saucer" ulcerated carcinoma.

Fig. 76A (left). Supine. A dense finger-like intrusion (arrow) into the gas column is evident in the region of the re-entrant angle. In addition, a sharp edge (arrow) traversing the entire width of the column is seen at the level of the distal margin of the defect. Poorly demarcated fainter soft tissue densities are seen lateral to and above the defect.

Fig. 76B (right). Barium meal examination shows, with compression, a ring-shaped defect with an ulcerated center. The exact appearance of a lesion of this type is most difficult to recognize on simple films since an en-face view is rarely obtained.



Fig. 77. Supine. Ulcerated carcinoma. Carman sign. The general course of the gas column is not remarkable. However, a large meniscus-shaped collection of gas (arrow) in the region of the re-entrant angle is separated from the lumen by a thick collar of soft tissue with irregular margins. In other words, a large filling defect, broad based on the lesser curvature, is present within which there is an ulcerated center of characteristic configuration.



Fig. 78. "Saucer" ulcerated carcinoma.

Fig. 78A (left). Supine. Gas is trapped in the proximal part of the stomach in a bizarre configuration. The normal locus is likely to be the denser lateral and superior collection. The "waisting" (arrows) of the column distally suggests tumor edges.

Fig. 78B (right). Barium meal examination demonstrates a neoplasm consisting of an elevated rolled border and ulcerated center. The "waisted" collection of air corresponds to the ulcerated center.

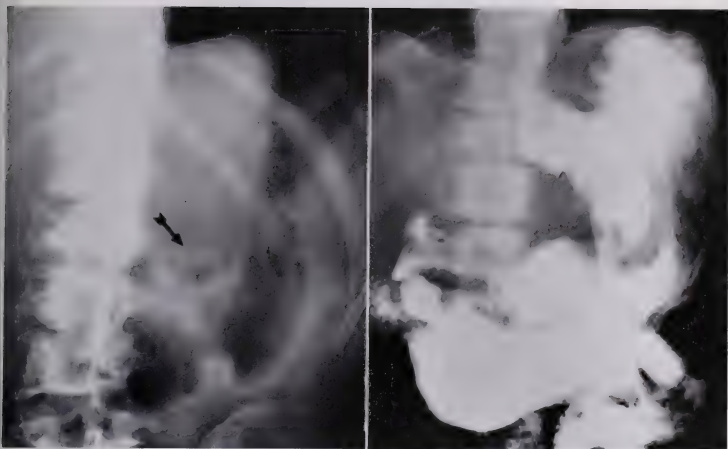


Fig. 79. Hodgkin's disease of the stomach.

Fig. 79A (*left*). Supine. The distal portion of the gas-filled stomach is not remarkable. Proximally, the gas occupies only the lateral portion of the stomach and shows a markedly irregular medial border. Gas is trapped in an irregular collection (arrow) extending well beyond the lesser curvature within a soft tissue mass. Incidentally, sclerotic destructive lesions are present in the spine which, in this young individual, suggest the correct diagnosis.

Fig. 79B (*right*). Barium meal done several months after Fig. 79A shows massive infiltration of the proximal portion of the stomach with a huge crater within a mass at the re-entrant angle.



Fig. 80A. Prone. Hodgkin's disease. A huge thickening of the lesser curvature aspect of the stomach compresses the lumen (lower arrow) to a thin gas column and simulates a scirrhus carcinoma. With the mass, however, small collections of trapped gas are evident (upper arrow) and the decrease in caliber is at the expense of the lesser curvature only.

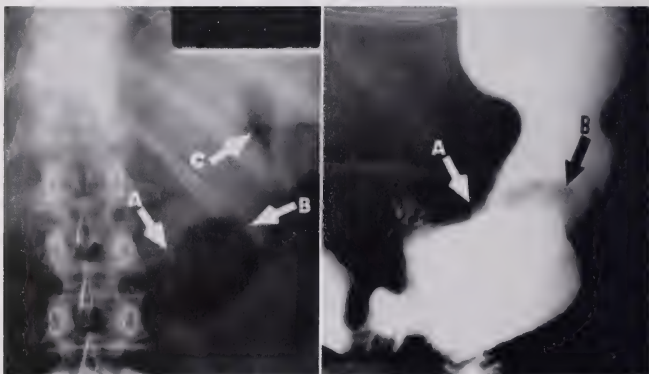


Fig. 80B (left). Supine. Another case; lymphosarcoma. Most of the gas in the stomach forms an ovoid sharply demarcated collection in the body of the stomach. This collection is remarkably lucent and the contour in places is flat or bulges towards the lumen (arrows A and B). Gas is also trapped in the fundus which is narrowed or compressed medially (arrow C).

Fig. 80C (right). Barium meal shows that the large collection of gas on the simple film (Fig. 80B) occupies a crater with irregular margins (arrows A and B). The overall caliber of the stomach at the site of ulceration is not decreased. The mass suggested on the simple film compressing the fundus medially was not clearly seen during the barium meal but a large mass of nodes was found at exploration in this region.

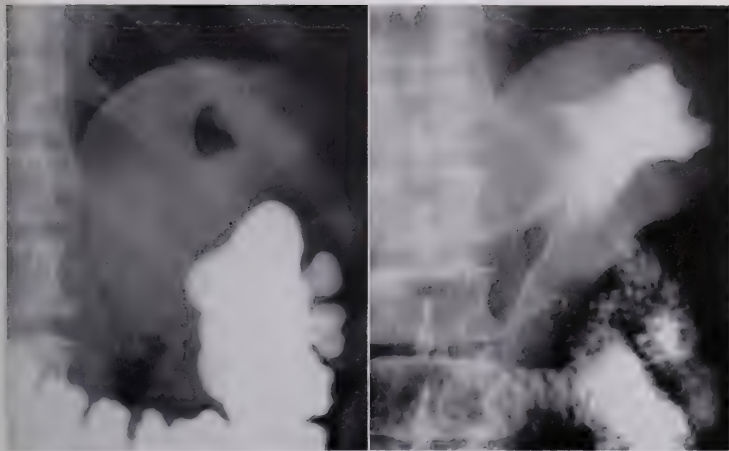


Fig. 81. Lymphosarcoma.

Fig. 81A (*left*). Prone. Film taken during barium enema shows a small collection of gas in the fundus with nodular protrusions laterally and inferiorly and an unusually sharp, punched-out border medially. Beyond the medial border, mottled contents can be seen and followed distally into a faint narrow gas column.

Fig. 81B (*right*). Barium meal shows a huge multinodular neoplasm occupying the proximal two-thirds of the stomach. Note the large distance between the lumen and the gas in the splenic flexure.

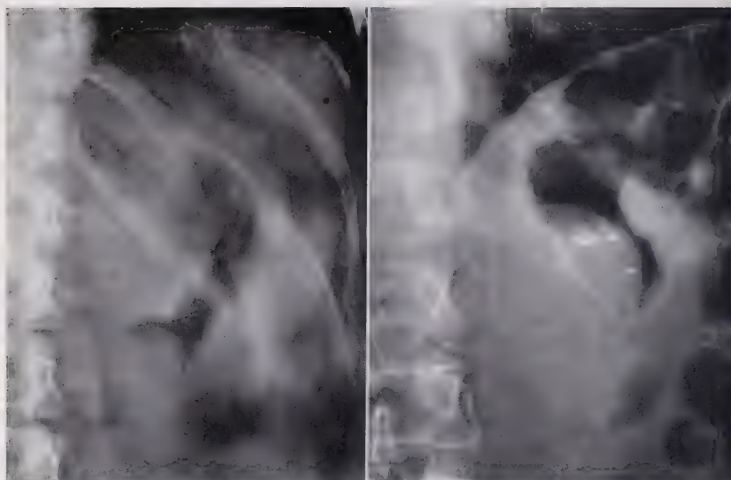


Fig. 82 (*left*). Supine. Intramural tumor. The gas column in the proximal part of the stomach is sharply cut off distally by a broad hemispherical protrusion which prevents the gas from entering the distal part of the stomach. The transverse diameter of the lumen is increased at the site of the mass.

Fig. 83 (*right*). Prone. Myoma. A smooth sharply demarcated hemispherical filling defect protrudes into the gas column from the lesser curvature below the cardia. Residual barium fills several deep ulcers within the mass.

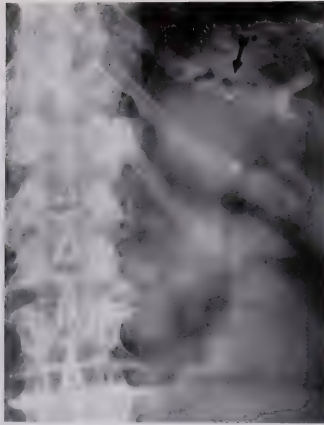


Fig. 84. Myoma.

Fig. 84A. Supine. The stomach contains a moderate amount of gas and fluid. Within the upper part of the fluid-filled fundus, a narrow crenated collection of gas (arrow) separated from the main column of gas is seen.

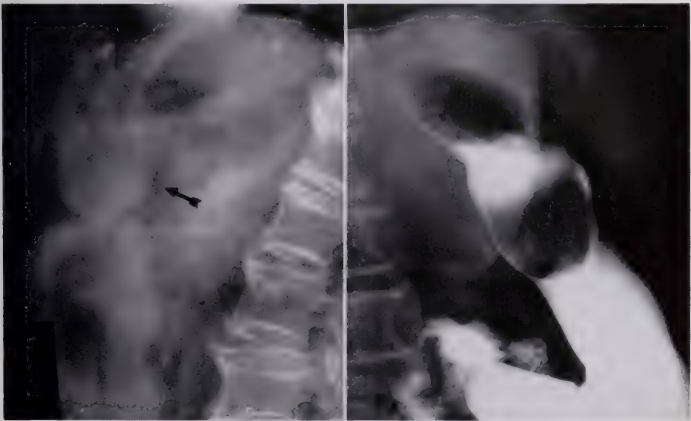


Fig. 84B (left). Lateral view of spine with patient lying on the right side was taken at the same time as Fig. 84A. An ovoid filling defect (arrow) with a smooth surface is outlined by surrounding gas. While some gas is present in the fundus above the mass, most of the gas is trapped distally at a lower level. This neoplasm was not recognized at this time.

Fig. 84C (right). Barium meal examination four years later shows findings typical of a myoma. Note again that the impression obtained from the simple supine film that the mass lies within the fundus is incorrect. It is located more distally, in the proximal portion of the body of the stomach.

III. BENIGN PEPTIC ULCER OF THE STOMACH*

The recognition of a peptic ulcer of the stomach on a simple film of the abdomen is possible when the ulceration is sufficiently deep to trap gas within it. Fortunately, the majority of peptic ulcers of the stomach occur along the lesser curvature which is presented in profile in the antero-posterior or postero-anterior projections ordinarily available. If the crater is small, it may appear as a small gas bubble to which little attention would ordinarily be paid (Fig. 85). Most small collections of gas which are seen in this area lie within the jejunum or the colon. It is necessary, however, to attempt to identify every such small collection in this region by noting its configuration and the nature of the surrounding shadows. The suspicion that a small collection of gas represents a gastric ulcer is of course strengthened if there is no evidence of any gas within adjacent loops of small bowel or colon. Of considerable additional assistance in many cases is the fact that unusual gastric functional changes appearing as abnormally distended or unusually contracted areas filled with gas and secretions are often present. These functional changes may quickly disappear during distension of the stomach by barium. When the crater is larger and the stomach contains sufficient air to outline the lumen, the picture of an ovoid or angular gas collection extending beyond the contour of the lumen of the stomach may be seen clearly (Fig. 86). A symmetrical neck between the crater and the general lumen of the stomach and an incisura on the opposite greater curvature complete the diagnostic criteria (Fig. 86). When a large amount of fluid is present in the stomach, gas caught between thickened rugae may be difficult to differentiate from gas within an ulcer crater. The gas between rugae ordinarily shows the typical undulating pattern and longitudinal course of normal rugae. In contrast, an ulcer crater is likely to be circular in outline or shows straight angular and sharp margins. Occasionally, the radiating pattern of thickened rugae can be suspected (Fig. 87). In most circumstances, the neck of the crater appears to be completely closed off from the lumen and separated from it by a rather distinct ledge of soft tissue (Fig. 88). Thick folds radiating to the lesser curvature may be seen during healing of the crater and simulate a filling defect (Fig. 89). It may be possible to recognize in such a case that the folds extend beyond the apparent defect for a considerable distance. In those instances associated with marked spasm, a most peculiar appearance may be evident which requires barium meal examination for elucidation (Fig. 90). Spasm of this type is frequently present in association with an antral ulcer (Fig. 91) and a small ulcer in this area is difficult to visualize. A large crater in this region, however, may be seen as a markedly lucent ovoid area within the narrowed antrum (Fig. 92).

Attempts to differentiate benign from malignant ulcers on simple films of the abdomen appear to be superfluous. In general a small crater which traps gas is much more likely to be benign particularly if there are obvious associated functional abnormalities. The presence or absence of evidence of a tumor mass is the most significant feature in differential diagnosis. The size of the ulcer crater is of relatively little importance (Fig. 93).

* Figures for this section appear on page 167 et seq.



Fig. 85. Prone. Benign peptic ulcer. Gas is trapped distally by a diffuse contracted segment occupying most of the body of the stomach. A discrete collection of gas (arrow) is located medial to the expected position of the stomach. Gas shadows in adjacent jejunum or colon are not seen. This was demonstrated to be a simple peptic ulcer by barium meal.



Fig. 86. Benign peptic ulcer at the re-entrant angle.

Fig. 86A. Barium meal examination shows a large ulcer crater (arrow) at the re-entrant angle with a broad neck. Thick folds radiate into the neck. (Round defect in the crater is presumably a foreign body.) The stomach contains a large amount of secretions and is unusually distensible.



Fig. 86B (left). Supine. Preliminary film shows the crater filled with gas projecting beyond the lesser curvature. The neck (medial arrow) of the pocket is faintly seen joining the dilated lumen of the stomach. The adjacent gastric wall shows a double slightly scalloped contour indicative of thick folds surrounding the neck. The greater curvature opposite the crater presents an incisura-like defect (lateral arrow) which was obliterated during the administration of barium. The features characteristic of benign ulceration are as clearly evident on the simple film as on the barium meal.

Fig. 86C (right). Supine. Film taken during barium enema also shows the ulcer crater (arrow). A large quantity of fluid is present in the dilated stomach and the gas column is interrupted, producing several discrete collections of gas trapped between rugae. In contrast to the crater, these follow the curvilinear course of the long axis of the stomach.

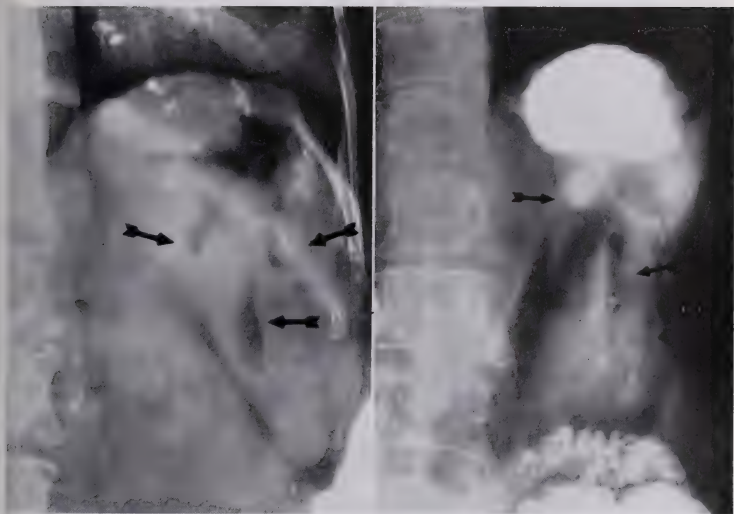


Fig. 87. Benign peptic ulcer.

Fig. 87A (*left*). Prone. The body of the stomach contains a considerable amount of fluid while gas distends the fundus irregularly and incompletely. Several discrete collections of gas are trapped distally. The lateral group (lateral arrows) show the typical scalloped contours of rugae which do not quite follow the usual curvilinear course. The medial collection of gas (medial arrow) has a "key-hole" configuration suggesting a round crater with a funnel-shaped communication with the general lumen of the stomach.

Fig. 87B (*right*). Barium meal shows a round crater (medial arrow) surrounded by a thick collar. The thick radiating folds between which gas was trapped on the simple film are evident (lateral arrow). Note that the barium has distended the fundus uniformly and obliterated the irregular contractility seen on the simple film.

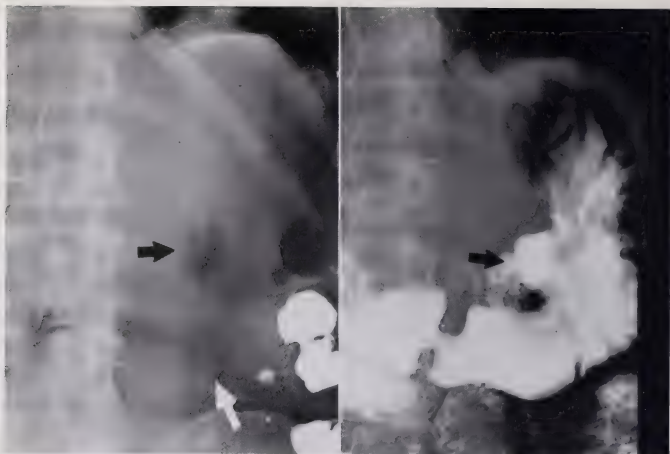


Fig. 88. Benign peptic ulcer.

Fig. 88A (left). Supine. A large angular collection of gas (arrow) is present in the region of the re-entrant angle. The stomach is faintly outlined by a thin mottled gas column floating on a large amount of fluid. Communication of the crater with the general lumen of the stomach is not evident.

Fig. 88B (right). Barium meal shows the identical configuration of the crater (arrow).

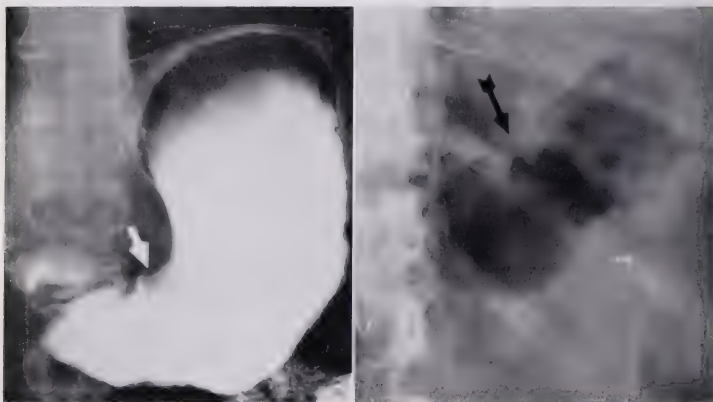


Fig. 89. Healed peptic ulcer.

Fig. 89A (left). Barium meal shows a broad fixed re-entrant angle (arrow) with thick folds radiating to this region.

Fig. 89B (right). Supine. Simple film. The defect or area of flattening (arrow) along the lesser curvature is clearly evident as are the thickened folds projecting into the gas column from this site. A shallow indentation covered by intact rugae is seen on the opposite greater curvature.

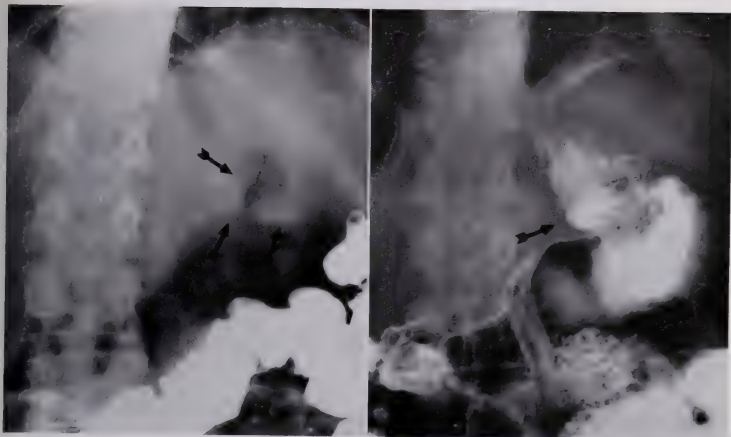


Fig. 90. Benign peptic ulcer.

Fig. 90A (*left*). Supine. Barium in the colon was administered prior to admission. Gas fills the distal half of the stomach but only a small irregular collection (arrow) is seen proximally. This collection joins the distal part of the stomach through a short channel. The soft tissue indentations around this channel suggest the margins of a mass but appear to be covered by normal rugal folds (lower arrows).

Fig. 90B (*right*). Barium meal demonstrates a round ulcer crater (arrow) corresponding to the medial portion of the irregular gas collection seen in Fig. 90A. The stomach wall around the crater and in the antrum is irregularly contracted and fails to distend.



Fig. 91. Benign antral peptic ulcer.

Fig. 91A (*left*). Barium meal shows an oval ulcer crater in the antrum with a collar-like defect around it due to inflammatory exudate and spasm.

Fig. 91B (*right*). Supine. The gas column shows an abrupt cut-off distally corresponding to the defect surrounding the ulcer. The ulcer crater (arrow) is seen a short distance beyond this. Deep peristaltic waves starting high on the lesser curvature are evident. These are unusual in the resting stomach and represent abnormal irritability. The feathery gas pattern medial to the stomach above the crater is characteristic of small bowel in the region of the ligament of Treitz.



Fig. 92. Benign large antral ulcer. Supine. Gas in the stomach delineates a rather diffusely narrowed antrum within which a markedly lucent oval collection (lower arrow) indicative of a crater can be seen. The lesser curvature of the more distensible proximal part of the stomach shows a nipple-like projection (upper arrow) which joins the general lumen of the stomach without any constriction or neck. This projection is not an ulcer crater but represents a functional abnormality associated with the ulcer in the antrum.

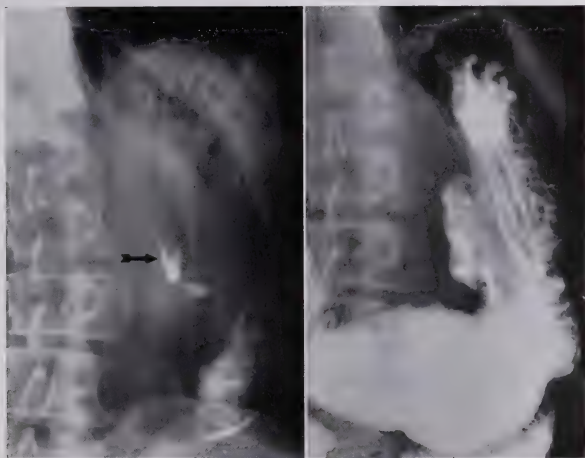


Fig. 93. Benign gastric ulcer.

Fig. 93A (left). Supine. The stomach contains a large amount of gas and some oral cholecystographic opaque material. Above the re-entrant angle, an elongated collection of gas distinct from the main gas column is seen. Some of the opaque material (arrow) has been trapped in this pocket.

Fig. 93B (right). Barium meal shows the full extent of the huge crater.

IV. MISCELLANEOUS GASTRIC LESIONS*

While tumors and benign ulcers form the majority of lesions of the stomach of intrinsic origin, a variety of other gastric abnormalities may occasionally be evident on simple films of the abdomen. It is not uncommon, for example, to recognize a herniated portion of the stomach if the lower mediastinum is included within a film of the abdomen and if the hernia happens to contain gas (Fig. 94). Ordinarily this occurs only with rather large hernias or with those of the paraesophageal type although occasionally a few bubbles of gas in the paravertebral region (Fig. 95) may be recognized in a hernial sac which is almost collapsed. A gas column which is continuous from the esophagus into the stomach is never seen under resting conditions. Gas may be trapped above the diaphragm not only in a hernial sac but also occasionally when a tumor mass is present in the distal esophagus (Fig. 96).

Under fortunate circumstances, an abnormal thickened rugal pattern in the antrum may suggest the presence of so-called hypertrophic gastritis (Fig. 97). Occasionally, thick folds may be seen extending through the pyloric ring indicating prolapse of gastric mucosa (Fig. 98).

The appearance of gas in the residual portion of the stomach after a subtotal gastrectomy may create confusion in the interpretation of simple films if a history is not available. In most instances, the residual portion of the stomach is not remarkably distended and little gas is seen in the recumbent position (Fig. 99). Occasionally the gas column shows an apparent abrupt distal cut-off (Fig. 100) which may simulate the presence of a filling defect. When this is associated with elevation of the adjacent portion of the transverse colon, the suspicion that a subtotal gastrectomy has been performed is confirmed. Obstruction in the region of the stoma or in one of the anastomatic loops after a subtotal gastrectomy may create confusing gas shadows which require a barium meal for elucidation (Figs. 101 & 102). This is also true with stomal abnormalities after gastro-enterostomy (Fig. 103).

The stomach may be involved secondarily by tumors arising in adjacent viscera particularly the pancreas. The roentgen findings on simple films of the abdomen will resemble those described for intrinsic neoplasms. Large tumor masses outside of but immediately adjacent to the stomach may produce marked displacement of the stomach (Fig. 104). In contrast to displacements by a hollow viscus such as a distended splenic flexure, a solid neoplasm ordinarily not only indents the adjacent wall of the stomach but dislocates the entire stomach in the compressed region.

* Figures for this section appear on page 175 et seq.



Fig. 94. Prone. A globular gas collection (upper arrow) is present in the mediastinum within a sliding hiatus hernia. Note the tapering deformity (lower arrow) of the fundus as it approaches the midline.



Fig. 95. Prone. The paravertebral shadow on the left (arrow) shows a bulging contour. Several faint icent areas in this region are due to gas in a herniated portion of the stomach.

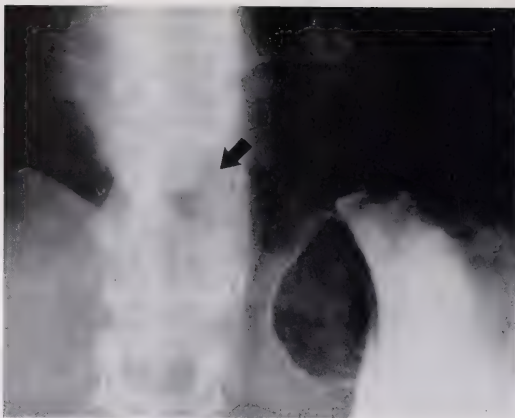


Fig. 96. Prone. Carcinoma of the esophagus. Gas is trapped between the diaphragm and the distal margin of a filling defect in the distal esophagus (arrow). The tumor was a large lobulated squamous cell carcinoma.



Fig. 97. Supine. The stomach is markedly distended with gas. Thick rugae project into the antrum (arrow) from both curvatures. The appearance on barium meal examination was similar, suggesting antral gastritis.

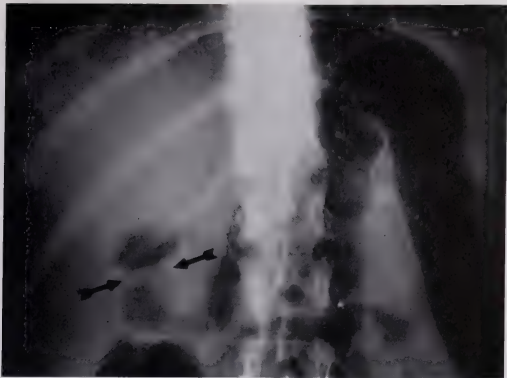


Fig. 98. Supine. A thick antral fold along the lesser curvature extends through the pyloric ring (between arrows) into the base or the bulb. Prolapse of gastric mucosa was confirmed by barium meal.



Fig. 99. Prone. Status post subtotal gastrectomy is indicated by the row of clips distal to the gas column. Note the limited distensibility particularly of the fundus.



Fig. 100. Prone. Status post subtotal gastrectomy. The residual portion of the stomach is distended with gas and shows an abrupt transverse distal cut-off. The scalloping of the distal margin, however, resembles thick rugae. The adjacent transverse colon is high and angulated towards the stomach as often seen after an antecolic gastro-jejunostomy.

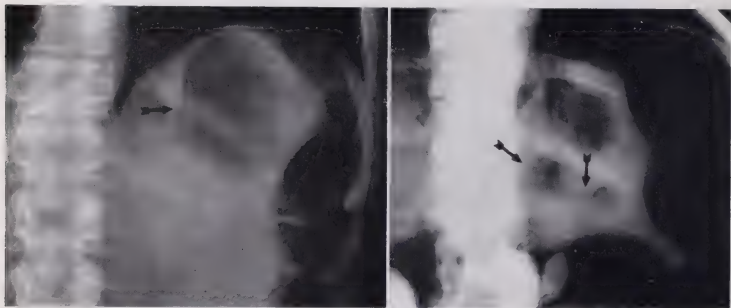


Fig. 101 (left). Prone. Status post subtotal gastrectomy. The gas-filled distended viscus below the left leaf of the diaphragm (arrow) shows a smooth contour with uniformly thin rounded upper margin. This was not the residual portion of the stomach but represented a partially obstructed afferent loop (as a result of recurrent reticulum-cell sarcoma).

Fig. 102 (right). Status post subtotal gastrectomy. A small residual portion of the stomach is seen immediately below the diaphragm. A peculiar transverse, dumbbell-shaped collection of gas is separated from the stomach by a thick fold (lateral arrow). This represented the site of anastomosis. The medial bulbous collection (medial arrow) was a large stomal ulcer while the lateral collection was in a kinked afferent loop.



Fig. 103. Status shortly post gastroenterostomy. The region of the anastomosis (arrow) appears quite dense with thick folds on both the gastric and enteric sides. The stomach proximal to the anastomosis is markedly dilated indicating the presence of obstruction. The short segment of anastomotic loop immediately below the stoma has a coarse mucosal pattern. (This film was part of an intravenous pyelogram which showed poor concentration by the left kidney).



Fig. 104. Large cortical adenoma of the left adrenal. Lateral view of spine. Right side down. The body of the stomach is displaced *in toto*, i.e. both the posterior and anterior walls, towards the anterior abdominal wall.

CHAPTER THREE

The Small Bowel

I. THE DUODENUM*

Under most circumstances, the duodenum does not contain a sufficient quantity of gas to permit satisfactory visualization. However, it is not uncommon for gas to be trapped in the duodenal bulb particularly when the patient is in the supine position. When the patient is placed in the prone position, the gas may persist in the duodenal bulb but often appears to enter the descending portion of the duodenum which may then be evident immediately to the right of the spine. The appearance of the duodenal bulb follows the general principle that, if it distends at all, it will assume a characteristic caliber and configuration (Figs. 105-107). The pyriform or triangular shape of the duodenal bulb may, however, not be evident because there is often extrinsic pressure by the liver or the gall bladder. Moreover, in the conventional antero-posterior projection, the duodenal bulb is ordinarily obscured by the overlapping antrum of the stomach, particularly if the stomach is transverse in position and distended. The base of the bulb when seen in profile shows a characteristic configuration convex distally with a dimple or triangular indentation in its center indicating the entrance of the pyloric canal. Exceptionally, the pyloric canal itself is evident as a result of a continuous gas column from the antrum into the bulb (Fig. 107). The most common abnormality which might be recognized in this area is, of course, duodenal ulcer. A characteristic deformity is rarely evident on a simple film of the abdomen presumably because an ulcerated bulb is ordinarily rather irritable, and rarely retains sufficient gas to permit satisfactory visualization. Nevertheless, on occasion, careful observation may demonstrate a faint gas shadow (Fig. 108) which outlines a deformed bulb. A deformity of the base of the bulb on a simple film is more commonly due to prolapse of gastric mucosa (Fig. 109) than to an ulcer. The existence of a duodenal ulcer may sometimes be postulated on the basis of so-called pyloric obstruction, particularly if there is evidence of deformity related to the bulb (Fig. 110). Gas confined to an ulcer crater within the bulb is rarely evident unless there has been a local perforation which has become sealed off (23) (Fig. 111A). In most instances, gas in the crater and in the deformed bulb are continuous, and the presence of the crater is difficult to discern (Fig. 111B).

Gas in the second portion of the duodenum with the patient prone ordinarily outlines the entire paravertebral or descending duodenum; division of the gas column into multiple segments is rarely seen in this area. As a result, the normal appearance is quite characteristic (Fig. 112). The most common abnormality which can be identified in this area is dilatation as a result of obstruction more

* Figures for this section appear on page 182 et seq.

distally situated in the duodenal sweep (Figs. 113 & 114). When this is marked, the duodenal bulb may also be unusually large. With the patient prone, the dilatation often appears to end to the right of the spine despite the fact that the obstruction may be situated in the region of the ligament of Treitz. This results from the compression of the transverse portion of the duodenum in front of the spine. In such instances, it can be demonstrated by placing the patient in the supine position that there is free communication between the dilated transverse portion of the duodenum and the descending part and that both are considerably distended. A moderate amount of dilatation of the second portion of the duodenum is not uncommon in the absence of an intrinsic lesion, presumably as a result of compression of the duodenum by the root of the mesentery. However, it is uncommon for the transverse portion of the duodenum to be markedly dilated in the absence of an intrinsic organic obstruction. Tumors of the duodenum, primary or secondary, are usually manifest only as a result of obstruction. In rare instances, the presence of a large mass in this area with a deformed gas column may be evident (Fig. 115).

Diverticula of the duodenum beyond the duodenal bulb are frequent and can often be identified on simple films. Characteristically, diverticula have a spherical configuration and are sharply demarcated peripherally without any septa or folds (Fig. 116). In some instances, the contents of a diverticulum become inspissated and have a mottled appearance (Fig. 117) which resembles fecal material in the right side of the colon. Occasionally, diverticula show a lobulated or arcuate configuration (Fig. 118) which may be difficult to interpret. The portion of the bowel from which the diverticulum arises may occasionally be seen immediately adjacent to it but the actual site of communication is rarely evident (Fig. 119). The duodenal bulb may also simulate a diverticulum but ordinarily its pyriform configuration will serve to distinguish it (Fig. 120).



Fig. 105A (left). Supine. The contracted pyloric region (arrows) protrudes into the base of the bulb which is directed medially towards the midline and partially overlaps the spine. The base of the bulb has a scalloped contour with a central indentation, resembling the cervical os.

Fig. 105B (right). Supine. Associated with gastric mucosal prolapse, the pyloric ring protrudes into the duodenal bulb. In an "en-face" view, this may simulate a polypoid or crescentic filling defect (arrow). Small gas collections within the defect lie between folds.



Fig. 106. Supine. The gas-filled duodenal bulb is immediately adjacent to gas-filled colonic haustra and may be mistaken for colon. The broad convex base of the bulb (arrow), however, is characteristic. Note the absence of valvulae within the bulb.



Fig. 107. Supine. The loculated gas collection high in the midabdomen consists of antrum and bulb separated by a patent short pyloric canal (arrow).



Fig. 108. Supine. Deformed bulb. A constriction in a poorly distended bulb is faintly seen (arrow). A normal duodenal bulb does not fill irregularly or "incompletely."



Fig. 109. Prone. An irregular gas collection in the right upper quadrant suggests a deformed duodenal bulb (arrows). On barium meal, however, only the base of the bulb was deformed by prolapse of gastric folds.

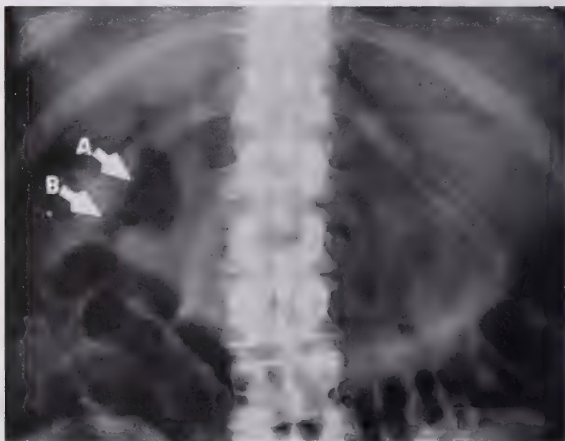


Fig. 110. Supine. The stomach is markedly distended with fluid. In the right upper quadrant, there is a pyriform gas collection (arrow A) which is continuous with a band-like shadow (arrow B). Ulceration and stenosis were present near the junction of the bulb (A) and descending duodenum (B).

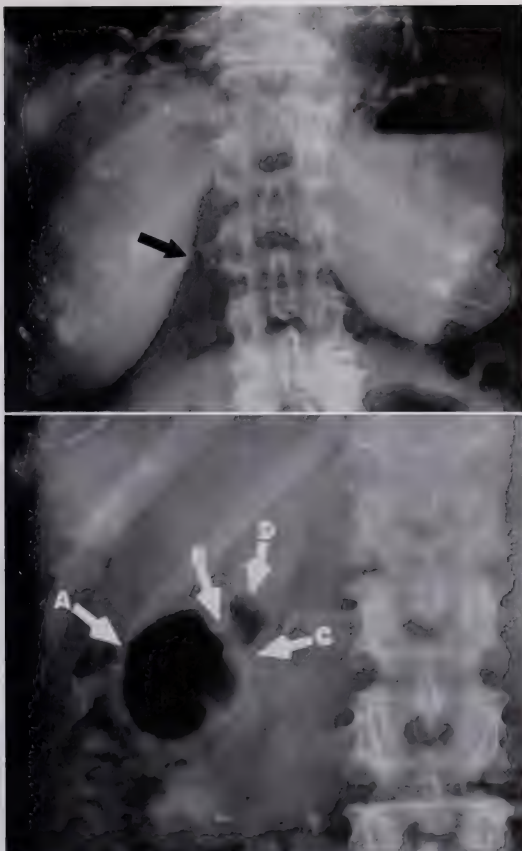


Fig. 111A (above). Erect. Sealed-off perforated duodenal ulcer. No free gas is present in the peritoneal cavity but, on close observation, an ovoid discrete bubble (arrow) is seen in the region of the bulb. The bubble was present in the same location on recumbent films as well.

Fig. 111B (below). Prone. In another patient, gas in the antrum (arrow A) continues through an elongated pyloric canal (arrow B) into a deformed bulb. A pocket with a small crater at its tip (arrow C) and a pseudodiverticulum (arrow D) opposite it were confirmed by barium meal.



Fig. 112. Prone. Gas in the descending duodenum (between arrows) outlines the typical location, calibre and configuration of this region. The prevertebral structures compress the distal margin.

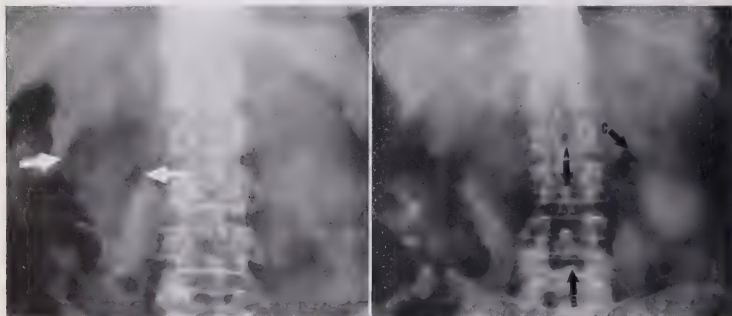


Fig. 113. Carcinoma of the pancreas with obstruction near the ligament of Treitz.

Fig. 113A (left). Prone. The descending duodenum (between arrows) is markedly dilated. The gas column can be followed proximally as far as the upper margin of the first lumbar vertebral but is obscured by fluid.

Fig. 113B (right). Supine. Fluid and gas in the duodenal sweep have exchanged positions and the dilated third or transverse portion of the duodenum is evident in front of the spine (between arrows A and B). The dilated duodenum ends abruptly in normal appearing undistended small bowel (arrow C) at the duodeno-jejunal flexure.



Fig. 114. Prone. Left anterior oblique. The descending duodenum (arrow) is markedly distended as a result of obstruction in the third portion of the duodenum due to involvement by metastatic peripancreatic nodes. The distal end of the gas column does not correspond to the site of obstruction.



Fig. 115. Carcinoma of the duodenum.

Fig. 115A (left). Supine. There is a large area of increased density to the right of the upper spine and moderate gastric dilatation. Faint linear arcuate gas shadows are noted superiorly (arrow A). In the center of the dense area, an irregularly narrowed gas column (arrow B) is a striking finding. The lower margin of the mass (arrow C) indents the colon.

Fig. 115B (right). Prone. Barium meal confirms the features evident on the simple film. The mass lies in the third portion of the duodenum (arrow B) but extends superiorly to and stretches the first portion of the duodenum (arrow A) and indents the colon inferiorly (arrow C).

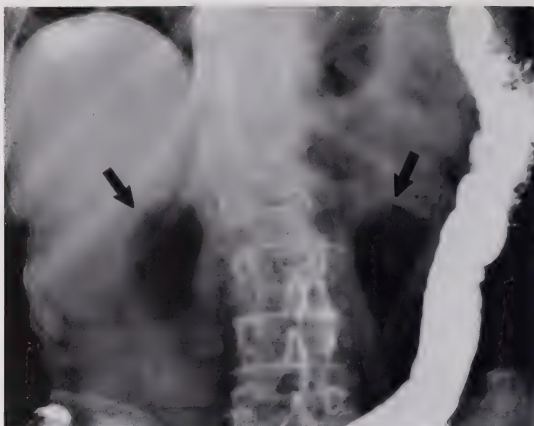


Fig. 116. Prone. Duodenal diverticula. On each side of the spine, sharply demarcated pyriform gas collections are seen which show no valvulae or septa. The tapering inferior portions can be reasonably related to the location of the duodenal sweep.



Fig. 117. Duodenal diverticulum. A large globular collection of mottled material (arrow) is present to the right of the upper spine. Inspissation of fluid contents has occurred within the diverticulum because of poor drainage.

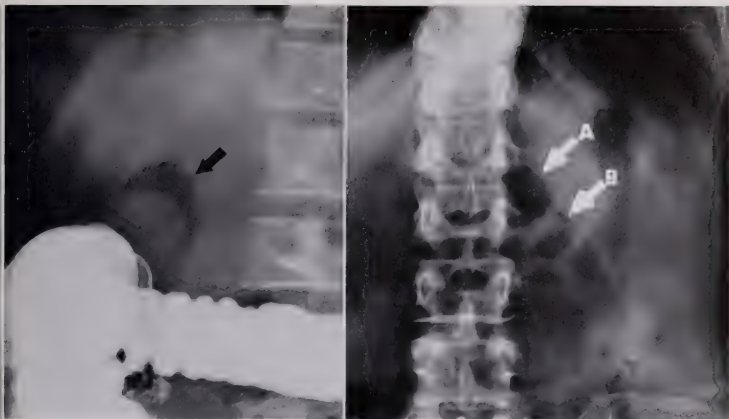


Fig. 118 (left). Duodenal diverticulum. A rather peculiar crescentic gas collection (arrow) is seen in the right upper quadrant. This was due to a large diverticulum which wrapped itself around the descending duodenum.

Fig. 119 (right). Supine. Diverticulum at the duodeno-jejunal flexure. Two collections of gas are present medial to the lesser curvature of the stomach. The superior collection (arrow A) is somewhat globular while the inferior (arrow B) is comma-shaped. Collection A is the diverticulum while collection B is adjacent small bowel. The neck or origin of the diverticulum is not evident.

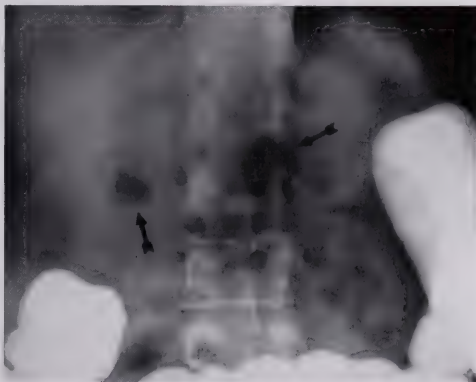


Fig. 120. Supine. Two discrete gas collections (arrows) are present in the upper abdomen. The globular collection in front of the spine is a diverticulum while the more triangular collection on the right is the duodenal bulb.

II. THE NORMAL MESENTERIC SMALL BOWEL*

Beyond the ligament of Treitz, the small bowel is attached to the free margin of the mesentery which projects into the peritoneal cavity from the posterior abdominal wall. Very roughly, the jejunum occupies the upper and left portion of the abdomen and the ileum the lower abdomen and pelvis (Fig. 121). The terminal ileum ascends across the brim of the pelvis and terminates at the ileocecal valve to the right of the sacro-iliac articulation. Loops of bowel high on the right side of the abdomen may represent distal jejunum, proximal ileum or, occasionally, terminal ileum. The lower right side of the abdomen, that is, the iliac fossa, is ordinarily occupied by the cecum and the proximal part of the ascending colon. Loops of small bowel rarely lie in front of or behind the colon in this area. This is presumably due to the fact that the normal mesentery and its attachment are not sufficiently long to permit small bowel loops to extend this far to the right and inferiorly. However, if the cecum is high in position and the viscera ptotic, loops of small bowel may occupy both iliac fossae in symmetrical fashion (Fig. 122). Since the upper loops of small bowel lie posteriorly, they cannot extend further superiorly than the retroperitoneal attachment of the transverse mesocolon (Fig. 123). When the gastrocolic ligament is long, however, loops of jejunum may be seen above the level of the transverse colon and below the stomach. These loops are then located behind the gastrocolic ligament and the transverse mesocolon. After operative intervention in which an opening has been made in the transverse mesocolon, for example, for purposes of gastroenterostomy, the anastomotic loops may occupy an exceptionally high position. The lateral extremities of the transverse mesocolon, that is, the peritoneal attachments of the hepatic and splenic flexures, may be sufficiently long to permit loops of small bowel to extend behind the flexures and reach a location above or lateral to the colon. Loops of small bowel may therefore intervene between the lateral abdominal wall and the ascending or descending colon (Figs. 124 & 125). In rare instances, small bowel loops may extend anteriorly in front of the colon and be interposed between the liver and the diaphragm (Fig. 126). In such cases, the mesentery of the small bowel must be unusually long.

Collapsed loops of small bowel or those that contain only the normal small amount of fluid are rarely evident as discrete shadows unless intraperitoneal fat happens to be unusually abundant. Occasionally, several loops may form a polycyclic density outlined against the properitoneal fat particularly in the left lumbar gutter. Some gas is practically always visible in portions of the small bowel, most commonly in the proximal jejunum and in the distal ileum. In the jejunum, the gas ordinarily is in the form of small collections caught between the redundant mucosal folds or valvulae conniventes. Often, apparently at random, a short segment of the small bowel is seen which is completely filled with gas. In such instances, the typical mucosal pattern of the small bowel will be visible along the margins of the gas collection and projecting into it. In the

* Figures for this section appear on page 193 et seq.

majority of cases, there is a surprisingly abrupt transition from the fluid content of the small bowel to the mottled semi-solid fecal material occupying the cecum and ascending colon. It is not uncommon, however, for the material in the terminal loops of ileum to show a mottled appearance with numerous discrete bubbles (Fig. 127) or occasionally larger quantities of gas, filling small segments of distal ileal loops. In these cases, it is likely that bacterial fermentation is active in the distal ileum as well as in the colon. Mottling elsewhere in the small bowel is abnormal.

As demonstrated by intraluminal pressure tracings, regularly recurring segmental contractions occur throughout the small bowel in both filled and emptied areas. These localized contractions cannot be recognized on simple films of the abdomen except under unusual circumstances. Nevertheless, their presence explains the fact that there is no free exchange of material in the small bowel with change in the position of the patient and that there is orderly progress of small bowel content in a proximal-distal direction. Normally, there is no continuous filling for any great distance of the small bowel by either gas or fluid. Rarely, multiple loops of small bowel in the left lumbar gutter may appear to be continuously filled with gas but these loops maintain a markedly tortuous and acutely angulated character (Fig. 128).

The small bowel hangs from the mesentery in groups of loops or coils. The limbs of individual loops are short and joined by hairpin turns; thus, normal small bowel has a markedly sinuous or tortuous course. The presence of frequent acute turns indicates normal pliability of the bowel wall. A long straight segment is therefore abnormal and this is true independently of the caliber of the segment, that is, whether it is distended or of normal or diminished caliber. Straightening of this type, with distension, occurs as a result of increased intraluminal pressure in obstruction. In the absence of obstruction, however, straightening is due to intrinsic involvement of the bowel wall and the consequent loss of pliability. The two limbs of a loop ordinarily diverge from each other, that is, the base of the loop is broader than the short curved connecting portion. A normal loop is not twisted; the two limbs do not cross each other. The small bowel loops adjust or mold themselves not only to each other but to adjacent intraperitoneal and retroperitoneal structures. As a result, indentations on the small bowel due to the colon, kidneys or psoas muscles are common. Loops of small bowel are relatively scanty in front of the spine and a segment of small bowel in the midline is usually transversely situated. A loop of small bowel in the pelvis is rarely vertically directed.

The characteristic caliber of small bowel when filled with gas or fluid is about two centimeters. It is slightly greater in the jejunum than in the ileum. It is quite remarkable how little the overall caliber of the small bowel changes during the progress of a motor meal. The fluid which enters a segment of small bowel often seems to replace, or rather efface, the redundant mucosa and submucosa which previously occupied the lumen. A filled segment shows a uniform caliber with a uniformly thin wall. The thickness of the wall can ordinarily not be judged unless there is an adjacent gas-filled viscus, since serosal fat is scanty.

There may, however, be sufficient fat in the mesentery particularly in the distal ileum to permit visualization of short segments of the outer wall of the small bowel.

Small bowel mucosal pattern consists of numerous plicae or valvulae conniventes (24) which are taller and more numerous in the jejunum than in the ileum. When a segment becomes markedly distended, many of the plicae or secondary folds are effaced. In the jejunum, thin valvulae recurring at short intervals and extending around the entire circumference always persist. In the excessively distended ileum, however, valvulae may be completely absent. The normal mucosal folds join the bowel wall at a right angle and are of uniform thickness. Because normal small bowel is so markedly tortuous, the valvulae are usually projected as curved lines. Adjacent valvulae may seem to cross or overlap each other for the same reason. True superimposition of loops, one on top of the other, is not common because of the limited antero-posterior diameter of the peritoneal cavity. While it is often difficult to judge the thickness of the bowel wall, the thickness of the mucosal folds seen in profile or projecting into the gas column is usually simple to evaluate. However, abnormally thick valvulae usually are also shorter than normal folds and project into the lumen for a shorter distance. As a result, they may be difficult to see through the gas column. Inflamed or edematous folds often appear to be blunted as well as shortened and may also be irregular in thickness and in height. The normal right angle at the point of attachment to the bowel wall is usually lost. Disease in or around the bowel wall is also indicated by irregular or eccentric distensibility. This is in contrast to the uniform distension or ballooning which occurs as a result of simple obstruction. If obstruction or a paralytic state persists, the bowel muscle may become "decompensated" and distension may then be irregular or erratic.

In contrast to adults, there is frequently a large amount of gas in the small bowel in infants and young children (25). If there is obvious distension of the bowel as well as continuous filling with gas, this is indicative of obstruction or ileus, as in adults. Electrolyte disturbances in children are particularly effective in producing abnormal small bowel patterns (26, 27), either distension with a considerable amount of gas or, in some cases, a complete absence of gas from the small bowel (Figs. 129 & 130).

Since the caliber of the lumen of the small bowel is relatively small, a faint and therefore shallow column of gas floating on liquid must be narrow. A hazy wide gas shadow in the course of the small bowel is abnormal. If such a gas shadow shows regular smooth or parallel borders, it is likely that it lies within a loop distended with a large amount of fluid. However, if the gas shadow is irregular with ragged margins, the possibility that it is located within a mass must be considered. This suspicion is strengthened if there is a sizable increase in density surrounding the faint gas shadow.

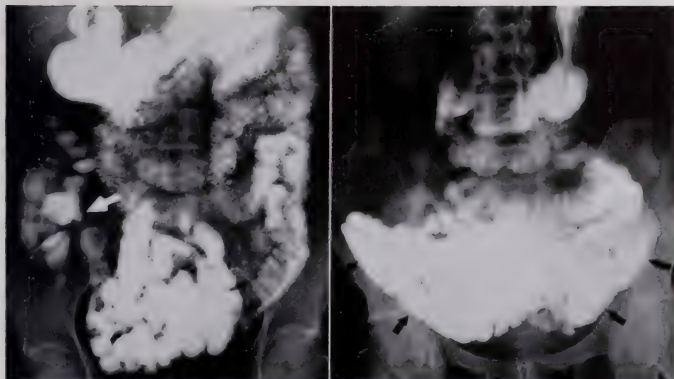


Fig. 121 (left). Supine. "Normal" location of small bowel loops; jejunum high and on the left, ileum low and on the right. The long axes of individual loops of jejunum lie in the frontal plane. The connecting limbs between the limbs of a loop are short and markedly curved. The loops in the pelvis are shorter, somewhat narrower and more crowded together. Except for the terminal ileum, no long vertical loop is present in the lower abdomen or pelvis. The ileocecal valve (arrow) is located high in the right iliac fossa.

Fig. 122 (right). Prone. Ptosis. Most of the small bowel is located in the lower half of the abdomen. Small bowel loops occupy both iliac fossae and the lateral limits of the peritoneal cavity are clearly indicated (arrows).

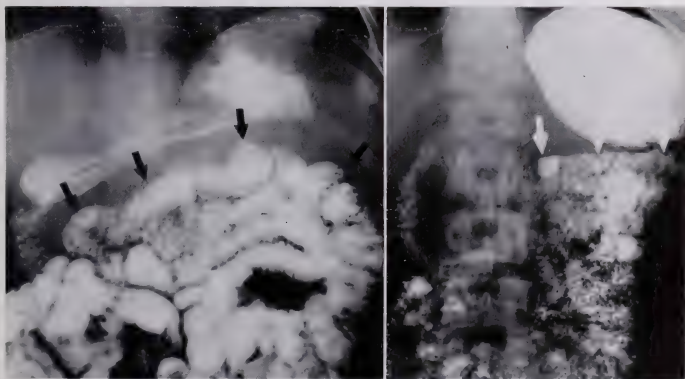


Fig. 123A (left). Supine. The retroperitoneal line of attachment of the transverse mesocolon is indicated the upper limit of small bowel loops (arrows).

Fig. 123B (right). Supine. In another patient, the superior excursion of jejunal loops is limited (arrows) an unusually straight transverse mesocolon.

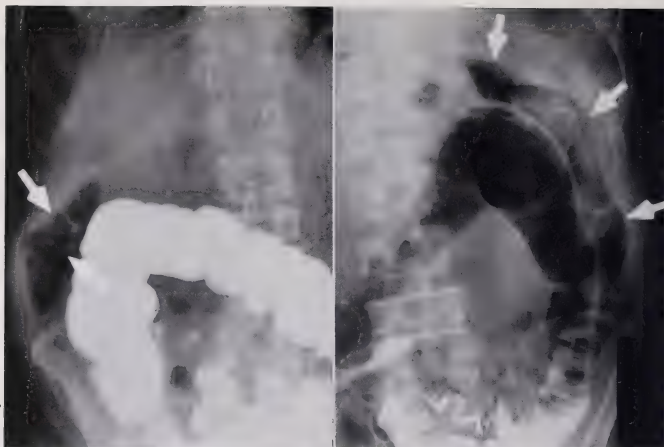


Fig. 124 (left). Prone. Small bowel (arrows) is present below the liver and between the lateral abdominal wall and the hepatic flexure of the colon. These loops have reached this region by extending behind the colon.

Fig. 125 (right). Prone. Small bowel loops (arrows) extend above and lateral to the splenic flexure and descending colon. These loops have extended posteriorly behind the colon.

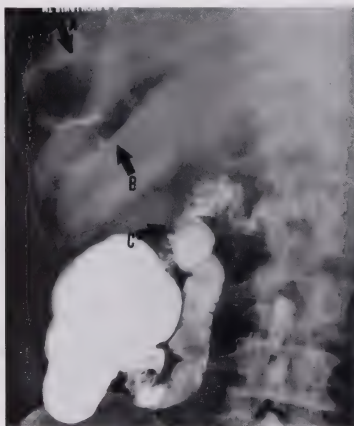


Fig. 126. Small bowel (arrows A and B) is interposed between the liver and the abdominal wall. The loop has extended anteriorly in front of the colon. The barium-filled terminal ileum is directed upward towards this area (arrow C).

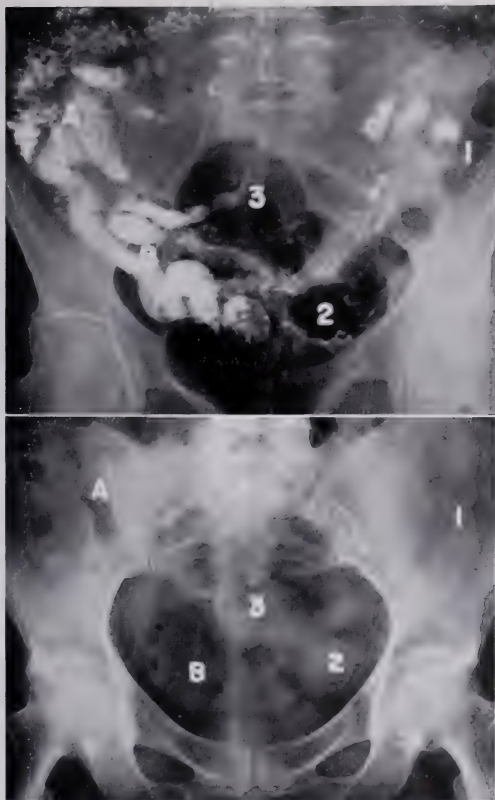


Fig. 127A (above). The ileocecal valve (A) is located high in the iliac fossa (see Fig. 121, also this patient). Ileal loops (B) occupy the right side of the pelvis with sigmoid above (3) and to the left (2) and ascending colon (1) normally located.

Fig. 127B (below). Supine. The mottled material on the right side of the pelvis (B) is located in loops of ileum. The colon (1, 2, 3) can also be visualized and contains relatively homogeneous material. The ileocecal valve (A) shows a typical beak-shaped configuration.

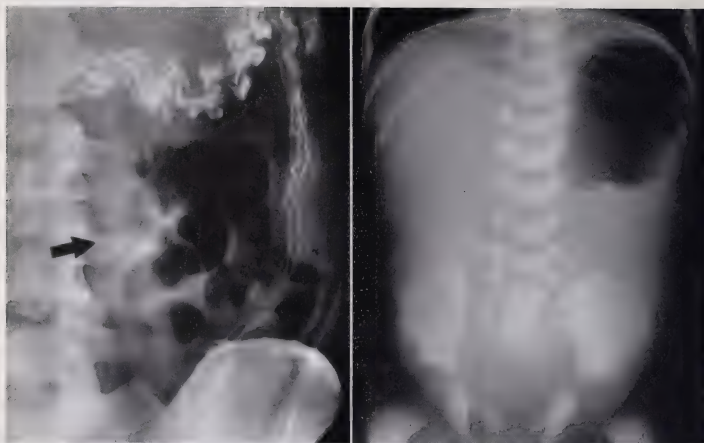


Fig. 128 (*left*). Prone. Short tortuous gas-filled loops of small bowel (arrow) are gathered together in the left lumbar gutter. There was no obstruction or internal hernia.

Fig. 129 (*right*). Except for gas in the distended stomach, the abdomen is empty of all gas and appears completely homogeneous. This child had severe diarrhea in the newborn period.



Fig. 130. Huge distension of small and large bowel is present in an infant with diarrhea and low blood potassium levels.

III. TUMORS OF THE SMALL BOWEL*

Tumors of the small bowel are notoriously difficult to detect both clinically and roentgenologically. Many of the tumors are lymphomata which do not ordinarily cause obstruction and which are therefore manifest clinically only as a result of bleeding, perforation or systemic symptoms. The finding of an abdominal mass frequently directs attention to the correct area in the abdomen if not to the correct viscus. In most cases, a barium enema and a so-called upper gastrointestinal series are performed prior to a small bowel series and therefore opportunities for observing abnormalities in the gas pattern of small bowel loops are frequent. A totally strange or bizarre collection, which can hardly escape attention, may be noted (Fig. 131). In other instances, however, careful search may be necessary to detect a faint irregular collection of gas (Fig. 132). Details may be so difficult to delineate that it is tempting to abandon the effort. Frequently, however, a similar abnormality can be found on several films and there may be additional findings, such as an associated mass density or signs of partial obstruction, which are helpful. In other cases, a large mass is evident because of displacement of adjacent viscera. Association with the small bowel may be difficult to recognize unless careful examination for collections of gas within the mass is made (Fig. 133). In the "aneurysmal" type of lymphosarcoma (28), there may be a marked increase in the caliber of the bowel at the site of the tumor and gas within the tumor may simulate a portion of the colon (Fig. 134). This resemblance is greater when the excavated center of such a tumor contains mottled material (Fig. 135). Tumors which encroach upon the lumen of the bowel (Fig. 136) may be recognized by a persistently narrowed gas shadow which is sharply demarcated proximally and distally by overhanging edges. In such instances, the findings are essentially similar to those described later in detail in the section on annular carcinoma of the colon.

As previously noted, a large number of tumors of the small bowel are sarcomata, frequently lymphosarcomata. Lymphosarcoma rarely produces intestinal obstruction unless intussusception has occurred. Hodgkin's disease of the small bowel may have an identical appearance to that of lymphosarcoma but is more often associated with narrowing of the bowel lumen which may produce complete obstruction. Benign tumors of the small bowel are rare. It is possible, however, to recognize a lipoma of the small bowel (Fig. 137) because of its unusual lucency and discrete nature.

* Figures for this section appear on page 198 et seq.

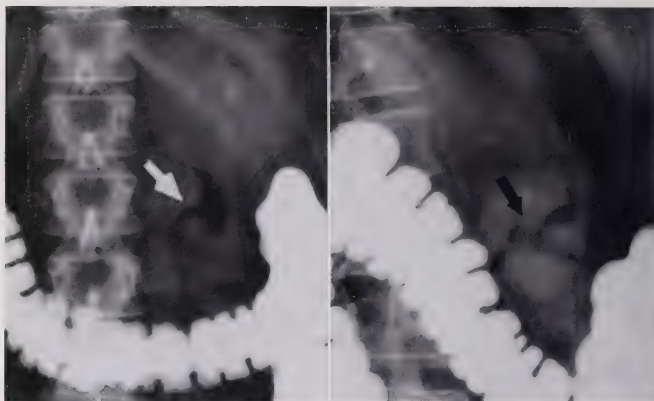


Fig. 131. Carcinoma of jejunum.

Fig. 131A (left). Prone. Barium enema is negative. However, medial to the splenic flexure, there is a stellate, sharply demarcated gas collection (arrow) which does not have the configuration of any normal hollow viscus. It resembles the renal pelvis and uretero-pelvic junction but the lateral border is convex, without evidence of calyces.

Fig. 131B (right). In the right oblique view, the bizarre stellate pattern is more marked (arrow) and extends beyond the kidney outline. A large multinodular carcinoma was located in the jejunum a short distance distal to the duodeno-jejunal flexure.



Fig. 132. Supine. Lymphosarcoma of jejunum. A ragged irregular gas shadow is present at the level of the iliac crest (arrow). There is a faint but definite increase in density surrounding the gas shadow forming a large ill-defined mass. In other cases similar to this, the gas shadow may be much fainter and require more careful search.

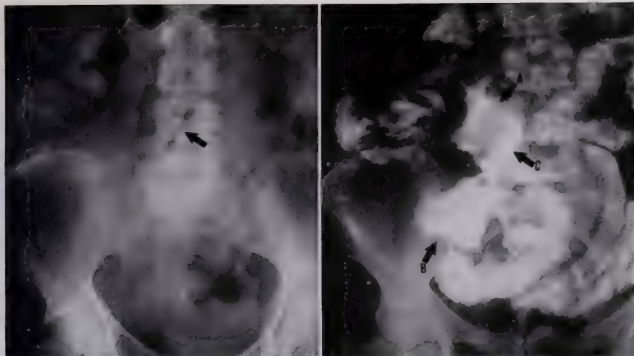


Fig. 133. Huge lymphosarcoma of the terminal ileum.

Fig. 133A (left). Supine. An ill-defined increase in density is present over the lower mid-abdomen. The fact that this is a large mass is indicated by absence of normal bowel shadows in this area. Within this mass, a slit-like gas collection (arrow) is present which indicates communication with the bowel.

Fig. 133B (right). Small bowel series shows huge excavations (arrows A, B, C) within the mass. The gas seen on the simple film occupied the periphery of one of these (arrow C).

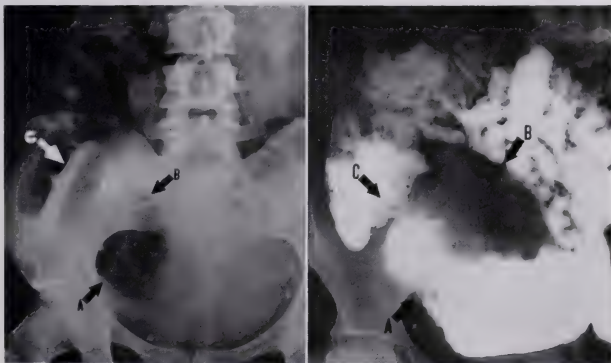


Fig. 134. Aneurysmal type of lymphosarcoma.

Fig. 134A (left). Supine. The caput coli appears to be remarkably well demonstrated (between arrows A and B) and sharp in contour. The borders of the gas shadow, however, show no septation or haustra, a thick transverse lip (arrow C) is difficult to interpret, and finely mottled contents extend beyond the gas shadow to the midline.

Fig. 134B (right). Small bowel series shows huge dilatation of the terminal ileum (arrow A). In addition, there is a wide space between the terminal ileum and adjacent loops of small bowel (arrow B), indicating the presence of tumor in and beyond the bowel wall. The lip (arrow C) represents edge of tumor intruding on the colon.

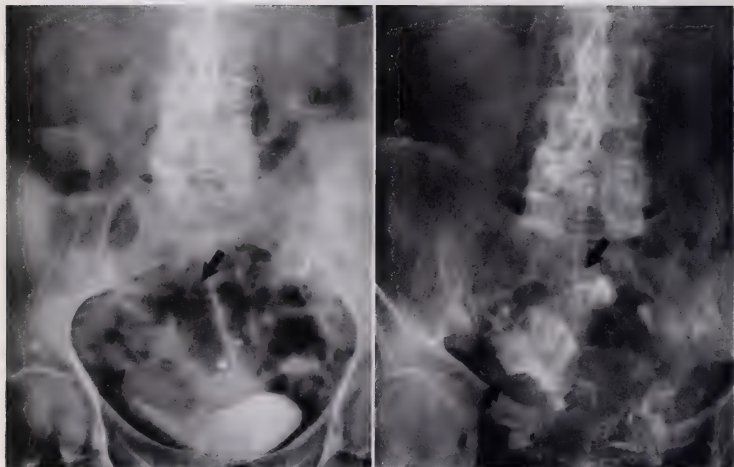


Fig. 135. "Aneurysmal" lymphosarcoma of terminal ileum.

Fig. 135A (*left*). Supine. A large irregular mottled gas shadow (between arrows) occupies the right side of the pelvis. This is easily mistaken for fecal material in the cecum. However, it is separated from the colon in the iliac fossa by a broad soft tissue density and no similar fecal material is seen elsewhere. The dome of the bladder (opacified during pyelography) is indented, with a broad soft tissue stripe between it and the mottled gas shadow.

Fig. 135B (*right*). Prone. Residual barium outlines a large ulceration or excavation (arrows) within the tumor in the terminal ileum. The caliber of the lumen is increased at the site of the neoplasm.

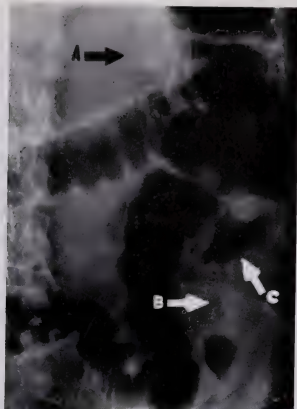


Fig. 136. Multiple lymphosarcomata of the small bowel.

Fig. 136A. Prone. Double contrast portion of barium enema examination. A peculiar gas pattern is present in the small bowel (arrows B and C) lateral to the descending colon. A faint thin channel (arrow B) connects two larger collections of gas. The superior collection shows a suspiciously sharp bulging edge (arrow C) which can be followed into the narrow channel. In addition, a faint dumbbell-shaped gas collection is present, medial to the splenic flexure (arrow A).

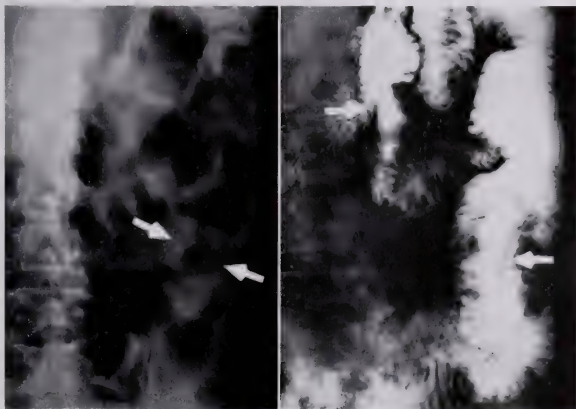


Fig. 136B (left). Supine. Four days later. An irregular collection of gas (between arrows) is again noted at the level of the iliac crest. The central portion is relatively wide with irregular nodular contours convex towards the lumen. The narrow superior portion abruptly joins dilated bowel, i.e., a sharp edge is present.

Fig. 136C (right). Small bowel series shows two narrowed segments (arrows) with ulcerated lumens and scalloped contours.

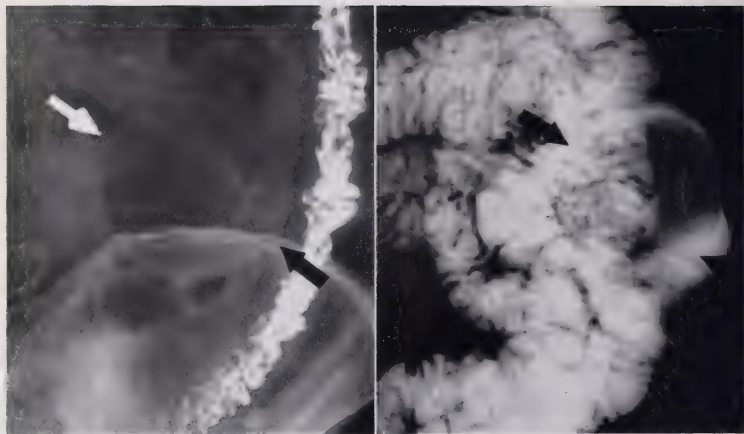


Fig. 137. Lipoma of jejunum.

Fig. 137A (*left*). Evacuation film of barium enema. A globular lucent area (between arrows) is present which is sharply demarcated around its entire circumference by a thin line of soft tissue density.

Fig. 137B (*right*). Small bowel series shows the large defect (between arrows) distending the lumen of the jejunum. There is no obstruction. Diagnosis was confirmed at operation.

IV. INFLAMMATORY DISEASE OF THE SMALL BOWEL*

The most common chronic inflammatory disease of the small bowel is *granulomatous* or regional ileitis, or ileojeunitis. In many instances, the disease is confined to the terminal ileum. In most cases, despite the fact that there is considerable thickening of the bowel wall, there is no fixed rigidity and the bowel lumen remains closed. Spasm resulting from increased irritability contributes to difficulty in maintaining filling. It is uncommon therefore to visualize persistent gas shadows in such diseased areas (Fig. 138). When there is sufficient obstruction, however, in the terminal ileum, the "preterminal" segment of ileum may be evident because of continuous gas filling. Since the disease ordinarily extends proximally into this loop as well, characteristic inflammatory changes may be recognized in this segment (Figs. 139 & 140). The presence of intrinsic disease is indicated by straightening and narrowing or irregular distensibility and the absence of a normal mucosal pattern. The thick mucosa produces hazy margins or double contours to the borders of the gas column. The increased thickness of the bowel wall and adjacent mesentery is identified by the fact that adjacent loops of bowel are separated from the diseased segment by a considerable distance. When the disease is extensive, this may simulate the presence of peritoneal fluid or exudate (Fig. 141). The involved segments of bowel frequently remain in the same position on serial examination or with change in position of the patient.

In *granulomatous jejunitis*, multiple short strictures with marked dilatation of the intervening portions of the small bowel are common. These intervening segments may be relatively short (Fig. 142) or markedly elongated with thick walls and thick septa resembling distended colon (Figs. 143 & 144). Thickening of the wall of these markedly dilated loops is the result of muscular hypertrophy due to long standing incomplete obstruction. The short narrowed segments of more marked disease intervening between the dilated portions may or may not be visible. In association with *granulomatous ileitis*, there may be large intra-abdominal masses due to marked involvement of the mesentery and nodes which compress or displace adjacent loops of small bowel or colon (Fig. 145).

Tuberculosis is a less common variety of chronic inflammatory disease of the small bowel and may be manifest by changes similar to those described above for *granulomatous ileitis*. The ileocecal region is frequently involved and a narrowed ileum and marked irregularity in the contour of the cecum and ascending colon may be evident on a simple film (Fig. 146). If there is an associated peritonitis or peritoneal reaction, the loops of small bowel may be separated from each other by increased gray stripes. In such instances, it is difficult to determine the extent of involvement of the small bowel since the loops fixed by plastic exudate may show a bizarre appearance.

In the more acute inflammatory diseases involving the small bowel, irregular distension with fluid and gas is commonly present as a result of functional disturbances. In severe cases, this may be combined with evidence of intrinsic disease of the bowel wall marked by thickening, irregularity or effacement of the mucosal pattern (Fig. 147).

* Figures for this section appear on page 204 et seq.

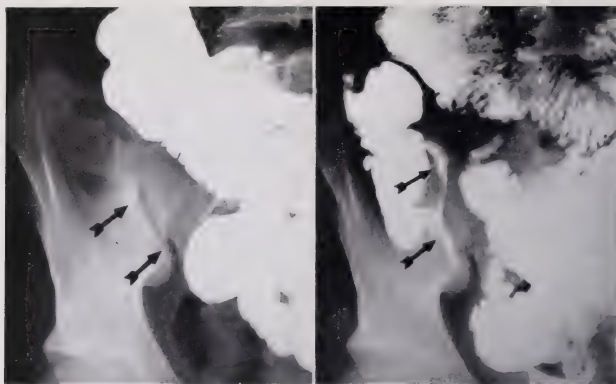


Fig. 138. Terminal ileitis.

Fig. 138A (left). Prone. Small bowel series—barium was delayed in entering the terminal ileum. The sacroiliac joint space (arrows) simulates a narrowed terminal ileum.

Fig. 138B (right). Prone. Later in the examination, barium in the terminal ileum (arrows) shows the narrowed, previously collapsed, terminal ileum.

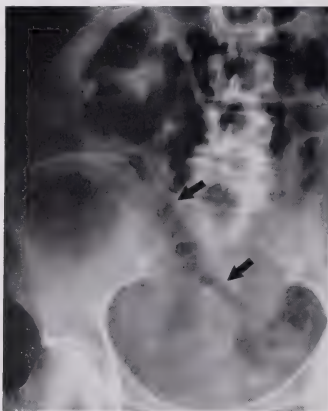


Fig. 139. Supine. Regional ileitis. An unusually long straight gas-filled segment of small bowel (arrow) is present low on the right side of the abdomen. The caliber of this segment is not uniform, the margins are indistinct and normal valvulae or mucosal folds are absent. A hazy density around this area suggests surrounding inflammatory reaction. This loop is situated above the usual location of the terminal ileum and represents a "preterminal" portion of distal ileum. The more dilated superior and lateral portion (upper arrow) is proximally located. The terminal ileum, which was more markedly involved, is not evident.

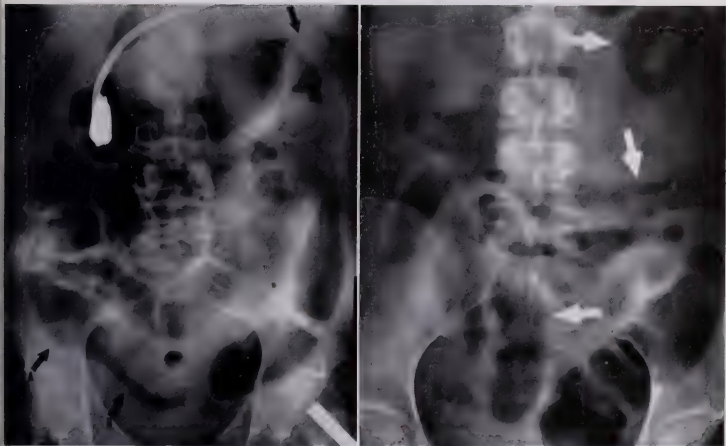


Fig. 140 (left). Supine. Regional ileitis and ulcerative colitis. A segment of small bowel proximal to the terminal ileum (arrows A and B) has a peculiar configuration—the proximal portion (arrow A) is dilated and the distal part (arrow B) is narrow. The mucosal surface distally is hazy with multiple irregular contours. The wall bulges towards the lumen; adjacent loops of bowel “avoid” the area. The wall of the dilated proximal portion does not appear to be thickened. Several uniformly dilated and normally sinuous loops of small bowel are present in the mid-abdomen. There is also an abnormal pattern of the gas in the colon; the distal transverse colon is dilated with an apparent stricture in the splenic flexure (upper arrow).

Fig. 141 (right). Supine. Ileojejunitis. Numerous gas-filled loops of small bowel throughout the abdomen (arrows) have an abnormal configuration and caliber. In the pelvis, the bowel is somewhat dilated, with thick walls; the loops at the level of the left iliac crest are narrow with thicker walls. The mucosal pattern shows no normal folds but is either totally absent (loop below the stomach) or irregularly flattened and scalloped. Other abnormal features include the lack of the normal sinuous configuration, unusually long and straight course, separation of loops, and the persistence of gas in the intrinsically diseased areas.



Fig. 142. Supine. Jejunitis. Short markedly dilated segments of bowel (arrows) in the left upper quadrant simulate the haustral pattern of colon. These are portions of relatively normal jejunum intervening between narrowed "skip" areas of granulomatous disease.



Fig. 143. Supine. Ileocejeunitis. Markedly dilated loops of small bowel filled with gas (arrows B and C) and fluid (arrow A) occupy the lower and left side of the abdomen. These loops are uniformly distended with minimal evidence of intrinsic disease. The bowel wall is uniformly thickened as judged by the width of the gray stripe intervening between loops A and B. In view of the marked distension, this gray stripe would be very thin if the bowel wall were normal. Barium meal examination showed multiple narrowed "skip" areas of granulomatous disease which are not evident on the simple film.



Fig. 144. Supine. Jejunitis. A hugely distended loop of bowel in the upper and left side of the abdomen simulates colon. Typical small bowel valvulae are present, however, in the loop on the left and the visualized portions of the colon do not appear remarkable. The bowel wall is thick (gray stripe between arrows A and B) despite marked distension, as a result of long-standing obstruction. The site of obstruction is not outlined but close observation shows an abrupt narrowing and flattening (arrow C) of the gas column in front of the spine due to intrinsic disease.



Fig. 145. Prone. Ileocolitis. The ascending colon is irregularly narrowed and shortened. It is also compressed on its medial aspect (arrow). No loops of bowel are evident in this area but there is a suggestion of an increase in density. Small bowel series showed extensive ileitis with large extrinsic masses displacing both small and large bowel.



Fig. 146. Supine. Ileocecal tuberculosis. Numerous loops of distended gas-filled small bowel occupy the mid-abdomen. The soft tissue stripes between adjacent loops are thickened (peritoneal exudate?). The gas pattern in the right lower quadrant outlines a narrowed terminal ileum (arrows B and C) and a markedly irregular cecum and ascending colon (arrow C). The ileocecal valve is effaced and patent.



Fig. 147. Acute necrotizing enterocolitis.

Fig. 147A (left). Supine A bizarre pattern of gas and fluid-filled areas of small and large bowel is noted throughout the abdomen. Small bowel loops (arrows) are moderately distended with coarse valvulae and coarsely scalloped borders.

Fig. 147B (right). Five days prior to 147A. Irregular distension with gas and fluid is more clearly evident on an erect film. Several loops of small bowel show a coarse valvular pattern (arrows) and eccentric flattening or limited distensibility along one border.

V. VASCULAR DISEASE OF THE SMALL BOWEL*

The recognition of mesenteric occlusion with infarction of the small bowel on simple films of the abdomen is well established and the roentgen findings are well known (29, 30). In a classical example, there is extensive involvement of the small bowel with hemorrhagic thickening of the wall and absence of normal motility. The most severely involved loops are narrowed with irregularity or scalloping of the walls and marked thickening of the wall as evidenced by separation of adjacent loops (Fig. 148). In the early stages (Fig. 149) or in cases with less severe damage, the changes in the bowel wall may be more difficult to identify. In most cases, many feet of small bowel are involved because of closure of the main vessel. In a limited number of instances, a relatively short segment is involved either originally or during recovery from more extensive vascular compromise (31, 32) (Figs. 150 & 151). The roentgen changes in these more isolated or discrete segments of bowel are similar to those seen with more extensive involvement. The most common type of segmental infarction of the bowel occurs in association with intestinal obstruction due to adhesions which produce a localized volvulus or closed loop (Figs. 152-154). Vascular compromise of such a loop ranges from simple congestion and edema to complete necrosis and gangrene. The presence of an abnormal loop of this type can often be detected on simple films of the abdomen (33) but the exact stage of the process is difficult to determine (34). Somewhat similar changes may be seen in the small bowel as the result of ascites or adjacent inflammatory disease (35) such as a peritonitis (Fig. 155) or a retroperitonitis due to adhesions to a bare area post-operatively (Fig. 156). Such secondary or non-specific involvement of loops of small bowel is more common clinically than primary vascular disease because of the large variety of intra-abdominal inflammatory conditions.

* Figures for this section appear on page 210 et seq.



Fig. 148. Supine. Extensive small bowel infarction due to mesenteric occlusion. Long parallel loops of small bowel (arrows) are seen in the mid-abdomen. These loops are narrowed with an irregularly coarsely serrated contour and separated from each other by hugely thickened soft tissue stripes.

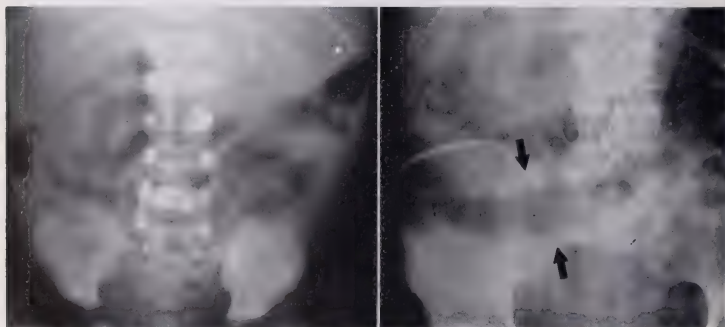


Fig. 149 (left). Infarcted small bowel in an infant due to volvulus. Gas outlines numerous loops of small bowel. In an infant, the presence of gas and the absence of a valvular pattern are not remarkable. However, these loops are not uniformly distended, lack normal tortuosity and are separated from each other by extraordinarily wide soft tissue stripes.

Fig. 150 (right). Supine. Localized small bowel infarction. A single elongated loop in the right iliac fossa (arrows) is dilated with marked irregular coarsening of the valvular pattern and separation from adjacent loops. At exploration, a foot of small bowel was gangrenous.



Fig. 151. Prone. Segmental infarction of the small bowel. A single loop of jejunum (arrow) shows a lack of normal valvular pattern with flattening of its borders and limited or irregular distensibility.



Fig. 152. Incarcerated gangrenous loop of small bowel due to post-operative pelvic adhesions. Dilated and fluid-filled loops of small bowel fill the abdomen. A discrete loop on the right side of the pelvis (between arrows A and B) is not markedly dilated but shows a thick irregular wall with no normal valvulae. The two limbs of the loop approach each other at its base (arrow C).

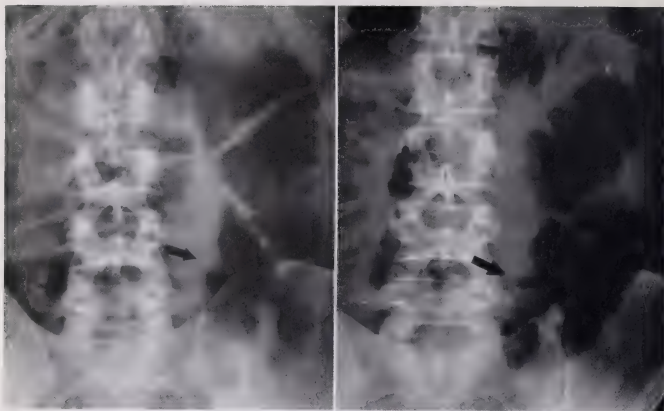


Fig. 153. Small bowel obstruction due to adhesions and a twisted loop.

Fig. 153A (*left*). Supine. The small bowel is dilated and filled with gas and fluid in continuous fashion. However, no loops are evident in the lower abdomen or pelvis and the site of transition can be located (arrow) approximately. The loop of bowel at this site shows an irregular contour with coarse folds.

Fig. 153B (*right*). Prone. Findings persist with change in position of the patient. At operation, a congested, edematous loop was found. It did not require resection.



Fig. 154. Supine. Small intestinal obstruction due to adhesions and a twisted loop. A horseshoe-shape loop (between arrows) is present on the right side of the pelvis. Valvulae are absent but the wall is smooth and does not appear to be thickened. The loop is narrow and the two limbs remain apposed to each other inferiorly at its base. At operation, lysis of adhesions was sufficient to restore a normal appearance to the bowel.

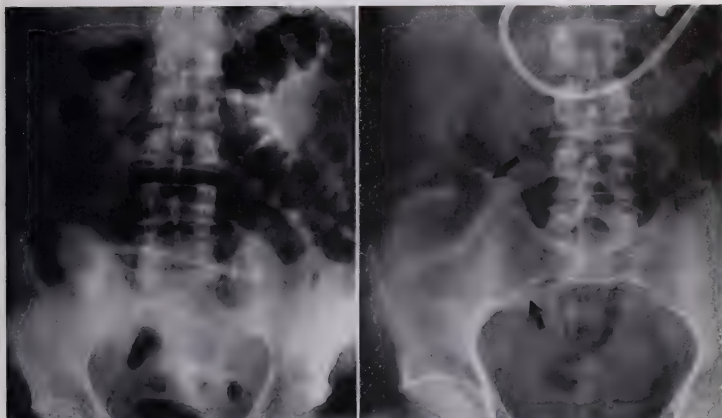


Fig. 155 (left). Supine. Acute appendicitis with perforation and peritonitis. Several long dilated transverse loops of gas-filled small bowel occupy the lower abdomen and pelvis. The thickening of the wall is partly due to serosal exudate or intraperitoneal fluid. Valvulae are present but difficult to visualize within the gas column because they project only a short distance into the lumen. This is indicated by the short blunt profile indentations. The valvulae in the dilated loop of jejunum on the left side of the abdomen are more normal in appearance but are also somewhat thickened and irregular. The colon in the right iliac fossa shows irregular distensibility and a soft tissue "gap" is present in the region of the appendix.

Fig. 156 (right). Supine. Incomplete obstruction post right colectomy. Irregular dilated gas-filled loops of small bowel are fixed retroperitoneally to the bare area produced at operation. Normal folds are absent and the wall shows faint scalloping. Two weeks after this film was taken, these loops showed a normal caliber and configuration but were still fixed in position.

VI. MISCELLANEOUS LESIONS OF THE SMALL BOWEL*

The characteristics of diverticula of the mesenteric small bowel are essentially similar to those described for duodenal diverticula (Fig. 157). Rarely, a duplication of the small bowel may communicate with the lumen, fill with gas, and resemble a diverticulum. However, a typical valvular pattern may be evident within a duplication (Fig. 158). Blind ends of small bowel after side-to-side anastomoses (Fig. 159) may also simulate diverticula but often are quite large and more cylindrical or tubular in configuration (Fig. 160). The relationship of a blind loop to the site of the anastomosis may be evident from the simple film or may require barium studies.

A large internal hernia may present as a confined group of fluid-filled (Fig. 161) or gas-filled (Fig. 162) loops of small bowel, in the absence of obstruction. The presence of a sac is indicated by the uniform convex margins of the trapped group of loops. If the afferent and efferent loops are also visualized (Fig. 162), the neck of the sac can be localized. In some instances, the presence of a para-duodenal or mesenterico-parietal hernia may be suspected by an indentation or displacement of the medial aspect of the descending colon (Fig. 163).

As pointed out above, mottling of the small bowel contents may be seen in association with diverticula or similar cul-de-sacs in the course of the small bowel or with an excavating or perforating tumor. Mottling of small bowel content in association with obstruction in the newborn period is characteristic of meconium ileus (36) (Fig. 164). Mottling of the small bowel content or abnormal small bowel content can also be recognized in patients with sprue of the tropical or non-tropical type. In such instances, there is usually dilatation of the bowel and a striking exaggeration of the valvular pattern (Figs. 165 & 166).

* Figures for this section appear on page 215 et seq.



Fig. 157. Prone. Large jejunal diverticulum. A globular thin walled structure (arrow) with no septa. A haustral pattern is present medial to the descending colon. Mottled contents can be faintly seen within it.

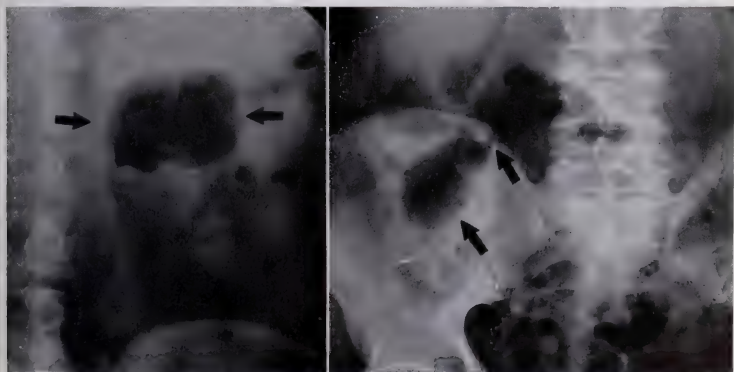


Fig. 158 (left). Supine. Jejunal duplication. A persistent, dilated, discrete, gas-filled structure (between arrows) in the left upper quadrant shows a valvular pattern. This was partially filled from the adjacent jejunum on barium meal studies.

Fig. 159 (right). Supine. Status post right colectomy and ileotransverse colostomy. A pear-shaped blind end of small bowel (lower arrow) is attached by a short stem (upper arrow) to the transverse colon.



Fig. 160. Status post ileotransverse colostomy and right colectomy. A large dilated blind loop (arrow) is present to the right of the spine, closed end directed upwards. The configuration of the loop does not suggest that it is ballooned under great pressure. The muscle in the wall is probably "decompensated," that is, maintains a large caliber with little increase in intraluminal pressure.

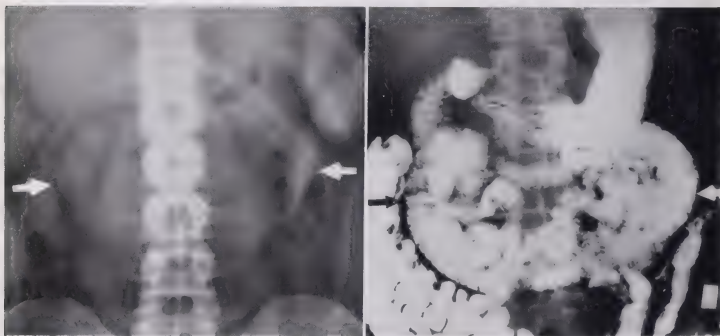


Fig. 161. "Paraduodenal" hernia.

Fig. 161A (*left*). Supine. A large bean-shaped sharply demarcated density (between arrows) occupies the upper mid-abdomen.

Fig. 161B (*right*). Prone. Small bowel loops between arrows are inclosed in a large internal hernia sac which extends both to the right and to the left of the spine above the transverse colon.



Fig. 162 (left). Prone. Left "paraduodenal" hernia. Gas-filled loops of small bowel occupy an internal hernial sac which extends behind the descending colon. The afferent (arrow A) and efferent (arrow B) loops approach each other as they pass through the neck of the sac.

Fig. 163 (right). Prone. Left "paraduodenal" hernia. The medial aspect of the descending colon shows an arcuate indentation (arrow) convex laterally. The region medial to the colon appears homogeneously dense due to fluid-filled loops of small bowel.



Fig. 164. Supine. Meconium ileus. Small bowel loops are distended with gas and, on the right side, contain mottled contents (arrow).

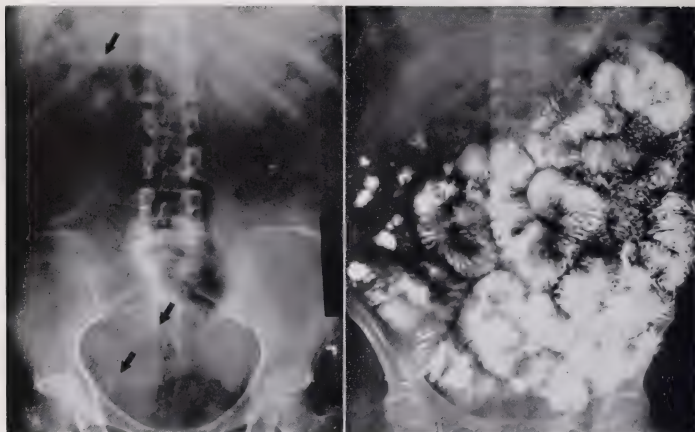


Fig. 165. Non-tropical sprue.

Fig. 165A (left). Supine. "Fecal" material high on the right side (upper arrow), on the left side, and in the pelvis has a finely mottled appearance. In addition, numerous, somewhat thickened, closely spaced valvulae are present in dilated segments of small bowel (lower arrows). Most of the "fecal" material is in the small bowel.

Fig. 165B (right). Prone. Small bowel series shows dilated small bowel with coarse valvulae. The valvulae are uniform in thickness and the small bowel loops show a normally sinuous course.



Fig. 166. Prone. Non-tropical sprue. Small bowel loops in the pelvis (arrow) are slightly dilated but the prominent feature is an exaggeration of the normal fold pattern with mottled bowel content.

CHAPTER FOUR

The Colon

I. THE NORMAL COLON*

The location of the various portions of the colon is basic information essential in the interpretation of any simple film of the abdomen. It is fortunate that gross abnormalities of position are uncommon. The normal variations in the course of the colon may, however, create considerable confusion since in contrast to a barium enema examination the entire colon is rarely visualized. An abnormally high cecum can sometimes be suspected by the absence of the normal colonic mottled fecal material from the right iliac fossa. More commonly, the cecum is low in position and extends into the pelvis. When uniformly filled with gas, the inferior rounded configuration of the caput coli can often be recognized, sometimes with a vertical haustral marking (Fig. 167). In rare instances, a retrocecal appendix directed superiorly contains sufficient gas so that it can be clearly identified (Fig. 168) (37). In most individuals, the transverse colon traverses the upper abdomen a short distance below the greater curvature of the stomach. In sthenic individuals, the transverse colon may occupy a level above the greater curvature of the stomach but this is unusual and associated with some degree of axial rotation of the stomach. In asthenic individuals, the transverse colon may loop markedly downwards and the distance between it and the greater curvature of the stomach may be quite large. In such cases, the adjacent limbs of the hepatic and splenic flexures may be almost vertical, and parallel the ascending and descending colon. The transverse course and the prominent haustral pattern of the transverse colon will ordinarily permit identification. The mid-portion of the transverse colon may show a rather localized acute angulation superiorly after an antecolic gastroenterostomy. When an angulation in this region is more marked and extends to the level of the diaphragm, the possibility of omental herniation into the mediastinum may be suspected.

With the patient in the recumbent position, some degree of interposition of the hepatic flexure of the colon between the liver and the anterior abdominal wall or the diaphragm is not uncommon. Interposition of the splenic flexure between the spleen and the left leaf of the diaphragm is rare. When the splenic flexure is distended, it may occupy the region immediately below the left leaf of the diaphragm but the spleen is then located posteriorly and medially. In the absence of splenic enlargement, the indentation on the superior and posterior lateral aspect of the splenic flexure by the spleen is ordinarily not marked. A flattening or an indentation of the hepatic flexure by the liver is common (Fig. 169) although a marked indentation of the gall bladder on the hepatic flexure is unusual.

* Figures for this section appear on page 224 et seq.

Considerable confusion may arise when there is a markedly elongated sigmoid loop which extends far towards the right side of the abdomen (Fig. 170) or extraordinarily high on the left side of the abdomen medial to the descending colon (Fig. 171). This confusion is often increased by the fact that such an elongated loop of sigmoid often shows a distinct haustral pattern resembling the more proximal portions of the colon.

There is ordinarily sufficient omental and mesenteric fat within the abdominal cavity to permit rather faint visualization of the outer wall of the colon when a gas-filled segment is present. A thin serosal fat line is rarely evident unless two such gas-filled segments are immediately adjacent to each other. In many individuals, there is a considerable amount of fat in the lumbar gutters continuous with the peritoneal fat. As a result, the outline of the descending colon both on its medial and lateral aspects (Fig. 172) and the lateral aspect of the ascending colon are ordinarily clearly evident.

The radiographic density of the bowel wall and of fecal material is essentially the same although occasionally inspissated fecal material appears to have a somewhat greater density. If a segment of colon appears to be uniformly and homogeneously dense with a relatively small caliber, it is likely that it is empty of fecal material (Fig. 172). If the caliber is large, it may be assumed that it is filled with fluid. As is the case with the small bowel, the overall diameter of the contracted or empty colon is greater than would be anticipated because of the marked redundancy of the mucosa and submucosa. In contrast to the small bowel, however, when the colon is filled under physiological conditions, the redundant mucosa becomes quite flat and, except for the haustral septa, the inner aspect of the colonic wall is usually quite smooth and sharply delimited. The characteristic caliber of the filled colon is at least twice as great as the small bowel. It is somewhat larger on the right side and in the transverse colon than in the descending colon and sigmoid. The caliber of the colon as filled physiologically is not greatly different from the caliber seen during barium enema examination despite the fact that the pressure applied by the enema is considerably greater. During filling, the thickness of the colonic wall does not appear to change remarkably until extreme distension is reached.

The classical pattern of the colon consisting of recurring haustra separated by thin septa is well known. These thin septa represent essentially twice the thickness of the mucosa with a minimal amount of submucosa. While there is little doubt that basically this pattern is anatomically determined, the formation of septa is also a functional phenomenon. Serial examinations of the abdomen taken, for example, during the course of intravenous pyelography often demonstrate the transient nature of haustral septa (Figs. 173 & 174). Haustral septa also disappear during a mass movement, not only in the contracting part of the colon but also in the area being filled. It has also been demonstrated that haustral septa may reappear after a period of several years in patients with healed ulcerative colitis (38). Moreover, many of the septa are thicker than those conventionally pictured in anatomical texts and presumably contain a portion of the muscular layer as well as mucosa and submucosa. These thicker septa have

been referred to as "muscular" haustral septa in contrast to the thinner "mucosal" septa. In addition to septa of these types, wider segmental contractions equal in length to one or several haustra which completely occlude the lumen are not uncommon (Figs. 173, 175 & 176). A concentric narrow channel may persist in a contracted area of this type (Fig. 175) or occasionally a haustrum, markedly narrowed from side to side, may be seen within its center (Fig. 176). In contrast to a haustral septum, the contracted bowel at the site of a segmental contraction may protrude into the adjacent haustra and simulate a filling defect (Fig. 176).

Intrinsic disease of the colon is often manifested by disturbances in the haustral pattern. Normally, haustral septa are fairly uniform in thickness although their luminal edges may show bulbous or club-shaped enlargements which may be bifid (Fig. 177). The haustra intervening between the septa bulge outwards in uniform fashion. When the haustral pattern is clearly evident, the short axial openings between adjacent haustra can often be visualized. The course of the longitudinal tenia intervening between the individual sacculations of the haustra (Fig. 173) can also be seen, sometimes completely separating the sacculi from each other. The sacculi of a single haustrum, particularly on the right side of the bowel, often appear to fill and contract independently of each other. This may be related to the "churning" action described as occurring in the colon. When the sacculi are not symmetrically filled, the openings in the haustral septa may be eccentrically located. The course of the longitudinal tenia then also appears to be eccentric and to parallel the openings in the haustral septa (Fig. 173).

Under physiological circumstances, free fluid in any large quantity is not present in any portion of the colon. In elderly individuals who evacuate poorly, fluid may remain in the colon after a cleansing enema. However, such individuals ordinarily do not tolerate an enema well so that any retention is ordinarily confined to the left side of the colon. It might be noted also that it is difficult to introduce any large quantity of air into the colon during the course of an enema because of the formation of a gas trap in the tube or in the rectum (10). After active catharsis, there may be considerable fluid in the colon, particularly on the right side, but this is not associated with dilatation (39). Under most circumstances, it is wise to assume that any substantial amount of free fluid in the colon is abnormal until proved otherwise. The recognition of even large amounts of fluid in the bowel on films taken with the patient recumbent may be difficult (Fig. 178A). This possibility, however, must be kept in mind when a wide homogeneous band-like density lies within the course of the colon and conforms to its anticipated location and configuration. In most instances, there is sufficient gas associated with the fluid to produce the typical appearance of a floating gas column (Fig. 178B). As elsewhere in the gastro-intestinal tract, a gas column provides the opportunity for visualizing the inner aspect of the bowel.

The fecal material in the right side of the colon shows a typical mottled appearance with innumerable trapped small collections of gas (Fig. 179). Mottled fecal material of the same character can occasionally be seen in the more distal portions

of the colon (Fig. 169). Material of this type is sufficiently pasty to form large continuous collections which are usually in contact with the bowel wall over a considerable distance. While this mottled fecal material is poorly demarcated, close examination of the periphery indicates that it fills the lumen in a fashion similar to fluid and that the contours bulge outwards and correspond to the expected colonic configuration. Larger discrete collections of gas are often seen adjacent to this fecal material but separate from it and rarely surrounding it completely (Fig. 180). In the normal progress of fecal material through the colon, most of the water is absorbed so that the fecal material on the left side of the colon is considerably more compact. Mottling is much less evident in the fecal material on the left side and may be completely absent. A reversal of the normal sequence, that is, mottled fecal material on the right side and fluid contents on the left side of the colon is abnormal. The solid nature of the fecal material in the left colon is often well seen when discrete collections are completely surrounded by gas and give the appearance of scybala. Such scybala may be mistaken for filling defects particularly if they are of homogeneous density (Fig. 181). Scybala are not seen normally on the right side of the colon. Marked scybala formation is unusual except in elderly individuals who presumably are chronically constipated. Commonly, the more solid collections of fecal material on the left side of the colon appear to alternate with short gas-filled segments. These gas-filled collections in the descending colon (Figs. 182 & 183) appear as discrete circular, ovoid or rectangular collections in the course of the colon. They ordinarily form a single column but occasionally a double column may be present if the haustral pattern is marked (Fig. 184). It is fortunately rare for any substantial amount of gas to be caught within this solid fecal material so that gross, totally bizarre, gas configurations do not occur normally. While discrete collections of gas may show a variety of configurations, the lateral bowel wall is usually convex outwards and is never convex towards the lumen. Along the axis of the bowel, however, the borders of these collections of gas are quite variable and may be straight, concave or convex. The variety of configurations along the axis of the colon is dependent on the nature and configuration of the segmental contractions which separate the colon into discrete compartments.

The appearance of the fecal material in the sigmoid corresponds to that seen in the descending colon. This portion of the colon, however, is the most difficult to visualize because of marked overlapping and the fact that under most circumstances it appears to be relatively empty. There is ordinarily some gas and fecal material to be seen in the rectum. This fecal material may be scybalous in nature (Fig. 185) or show a coarsely mottled appearance somewhat resembling the fecal material on the right side of the colon. When filled with gas, the configuration of the rectum may be quite bizarre (Fig. 186). This may be related to the fact that the rectum is the terminal portion of the colon where intraluminal pressures are variable and dependent to some degree on voluntary action.

With present knowledge, the amount of fecal material and gas in the different portions of the colon is unpredictable. However, nowhere in the course of the colon should there be any persistently narrowed channel outlined by gas. Be-

cause of the principles described in the first chapter, a narrowed segment of significant length must represent a transient phase during filling or emptying. Such transient phases are occasionally seen (Figs. 187 & 188) and often assume a rather bizarre dumbbell configuration. The narrowed segment in such instances is not associated with any proximal or distal edge and is not irregular or angular in outline. Occasionally, as pointed out above, a thin gas-filled channel along the axis of the colon may be seen intervening between two gas-filled haustra. This channel is uniform in caliber and centrally located. A discrete large collection of gas in the course of the colon is also unusual. Occasionally, however, a short segment of the colon may be ballooned in isolated fashion (Fig. 189) for no apparent reason or the apical portion of a redundant flexure may fail to contract and may retain gas (Fig. 190).

Under abnormal circumstances in which a large part of the entire colon is uniformly patent or in free communication, the distribution of fluid and gas will depend on the position of the patient and, in general, will follow the same physical principles that apply to the stomach. With the patient supine, gas will rise and fill the transverse colon. In this position, gas is ordinarily also trapped in the cecum and ascending colon as well as the distal descending colon and sigmoid. With the patient prone, fluid enters the transverse colon and gas enters the regions of the hepatic and splenic flexures, the distal ascending colon and the proximal descending colon. Because of angulation at the hepatic and splenic flexures, at the junction of the descending colon and the sigmoid, at the rectosigmoid and within a redundant loop of sigmoid, free exchange of fluid and gas between adjacent segments may be hindered or blocked by the formation of traps. The presence of such traps is often not immediately evident on a simple film but can frequently be surmised.

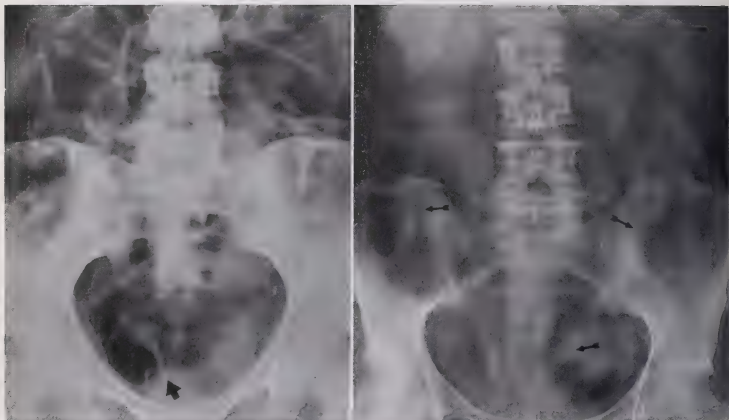


Fig. 167 (*left*). The gas-filled caput coli is low in the pelvis. The haustral septa are thin. A vertical septum (arrow) is present at the apex of the caput.

Fig. 168 (*right*). Supine. The appendix (arrow on right) is filled with gas and is directed upwards behind the colon. Loops of small bowel (arrows on left) are somewhat distended with gas and show an exaggerated coarse valvular pattern. This was the result of a sprue-like picture due to abdominal Hodgkin's disease.

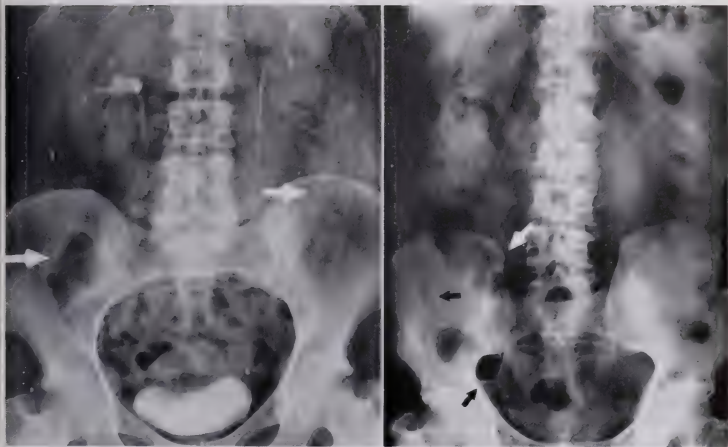


Fig. 169 (left). Supine. There is a flat indentation (arrow on right) on the lateral aspect of the ascending colon due to the liver. The descending colon (arrow on left) is filled with mottled fecal material in continuous fashion. Both the inner and outer surfaces of the bowel wall of this portion of the colon are evident.

Fig. 170 (right). Supine. A loop of bowel filled with gas is transversely located above the brim of the pelvis (white arrow). This is not the transverse colon which is located high in the abdomen at the upper margin of the film. This loop, when visualized as continuous with the other gas-filled segments (black arrows) in the right lower quadrant, can be recognized as an elongated sigmoid.

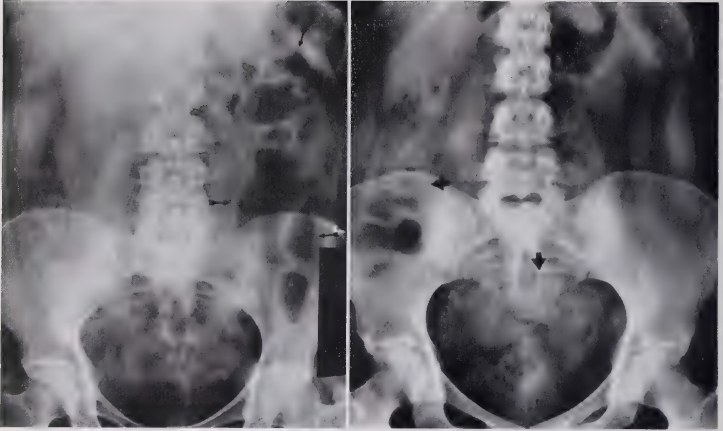


Fig. 171 (*left*). The apparent duplication of the descending colon (lower arrows) is the result of an elongated sigmoid extending into the left upper quadrant (upper arrow). The sigmoid is located on the inner aspect of the descending colon.

Fig. 172 (*right*). Supine. The descending colon is clearly seen as a vertical ribbon-like density in contrast to surrounding retroperitoneal fat. It is likely that this portion of the bowel is empty and collapsed. Gas in the caput coli fills subdivided haustra. In the ascending colon, the gas collections are probably bubbles in fluid-filled haustra. The lateral margin of the ascending colon is well seen against adjacent properitoneal fat. The medial margin of the ascending colon can also be faintly seen (arrow on right). The rectosigmoid (lower midline arrow) is distended with mottled semi-solid fecal material.

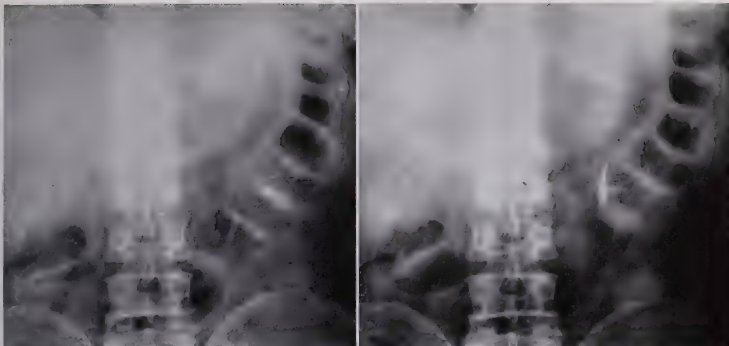


Fig. 173. Haustral and segmental contractions in the transverse colon.

Fig. 173A (*left*). Supine. The distal transverse colon is moderately distended with gas. Thin septa subdivide the lumen. The proximal margin of the gas column is arcuate in configuration.

Fig. 173B (*right*). Ten minutes after injection of contrast medium for intravenous pyelography, a remarkable change in the appearance of the distal transverse colon is noted. No thin septa are present but a thick bar of soft tissue completely divides the gas column distally. This bar represents a broad local contraction. The proximal margin of the gas column in front of the spine is tapering—a configuration which is not normally stable.

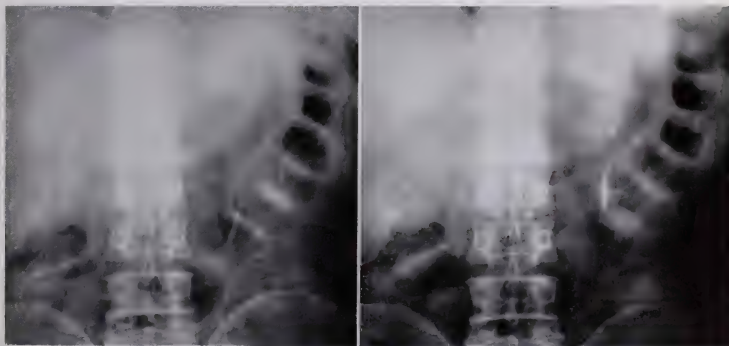


Fig. 173C (*left*). Ten minutes later, a characteristic symmetrical haustral pattern is seen throughout the distal transverse colon.

Fig. 173D (*right*). Ten minutes after 173C, the thick haustral septum immediately to the left of the spine has disappeared although its original site is indicated by shallow depressions on each contour. During the entire period of observation, a segment of colon in front of the spine remained contracted.

Note in Figs. 173C and 173D, the faint longitudinal linear density crossing the haustra and corresponding to the septal openings. This represents one of the tenia, presumably the tenia libera, on the anterior surface of the colon.

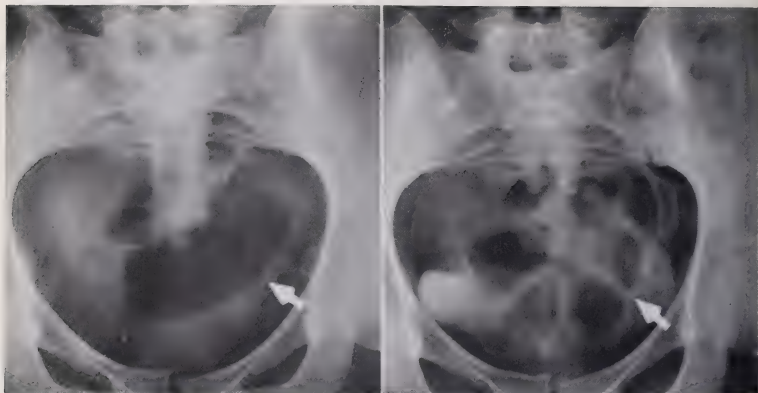


Fig. 174. Transient loss of haustral pattern.

Fig. 174A (*left*). Supine. Film taken prior to intravenous pyelography shows a gas-filled somewhat distended loop of sigmoid without any haustral pattern (arrow).

Fig. 174B (*right*). During pyelography, distinct haustral pattern with rather thick septa (arrow) appeared in the sigmoid.



Fig. 175. Supine. No intrinsic lesion. A thin central faint column of gas connects two haustra in the distal transverse colon (upper arrows). The "missing" haustrum is contracted and bulges into the adjacent haustra. The proximal margin of the gas column in the sigmoid tapers in an unusual fashion.



Fig. 176. Prone. Several gas-filled haustra are seen in the descending colon separately by relatively contracted segments. In the midst of one of these contracted areas (arrow), a thin almost completely collapsed haustrum is outlined by a small amount of gas. This haustrum is surrounded by soft tissue which protrudes into the gas column of adjacent haustra.



Fig. 177. Supine. No intrinsic lesion. The transverse and descending colon are moderately distended with gas. Several haustral septa show club-shaped free margins (arrows) which simulate small polyps.

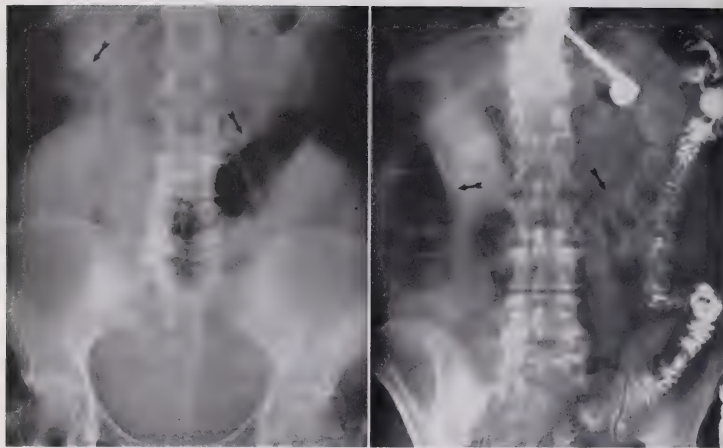


Fig. 178. Obstructing carcinoma of the splenic flexure.

Fig. 178A (*left*). Supine. An apparently discrete distended loop of bowel (arrow on left) filled with fluid is seen to the left of the spine. A rather homogeneous increase in density is seen throughout the left abdomen. A gas-filled haustrum (?) (arrow on right) is evident in the region of the hepatic flexure.

Fig. 178B (*right*). Prone. Immediate barium enema examination showed obstruction due to a stricturing carcinoma in the splenic flexure. It is now evident that considerable fluid is present throughout the colon proximal to the obstruction. The discrete gas collections (arrow on left) in the haustra of transverse colon are floating on fluid. The outer walls of the transverse colon are clearly delineated. The slightly arcuate septa project into the gas column within the distended ascending colon (arrow on right).

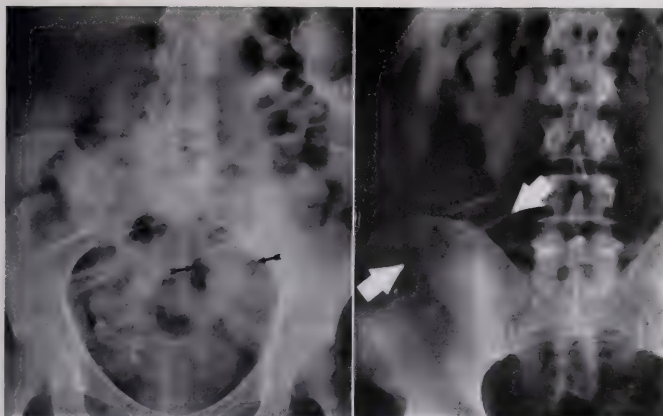


Fig. 179 (left). Supine. A large amount of mottled fecal material is seen in the cecum and ascending colon. Scybalae surrounded by gas are present in the descending colon. In the sigmoid, scybalous masses simulate a filling defect with overhanging edges (arrows).

Fig. 180 (right). Supine. Finely mottled fecal material fills the lateral portions of the cecum and ascending colon (lateral arrow) while gas occupies the medial portions (medial arrow). It is likely that the fecal material is sufficiently fluid to fall to the most dependent part.

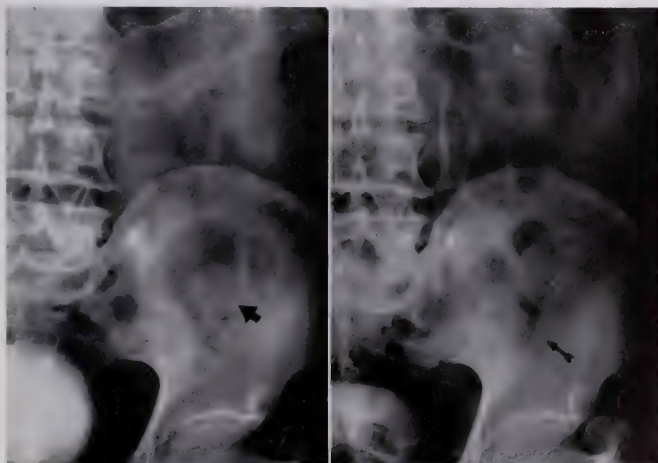


Fig. 181A (left). Supine. A scybalum (arrow) in the distal descending colon simulates a filling defect.

Fig. 181B (right). Same case, twenty minutes later. The apparent defect is more completely surrounded by gas (arrow) and is continuous with similar fecal material proximally.

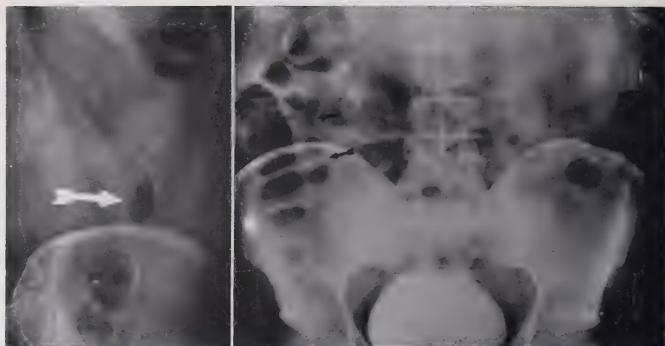


Fig. 182 (left). Supine. Normal. There is an elongated discrete collection of gas (arrow) in the descending colon which does not resemble a haustrum but is trapped between two contracted segments. The small bubbles above this area are probably trapped in solid fecal material (no preparation prior to examination).

Fig. 183 (right). Supine. The pattern of gas in the descending colon consists of discrete collections separated from each other by contracted regions of variable length. No septa are present within the individual gas collections. The lateral borders of each collection are flat or convex outwards. The axial borders are flat, convex or concave. A bizarre haustral pattern is present in the ascending colon—the lateral saccules are uniformly distended but the medial saccules (arrows) have a variable shape and size. While this is partly due to projection differences, the individual saccules of a given haustra may relax and contract independently.

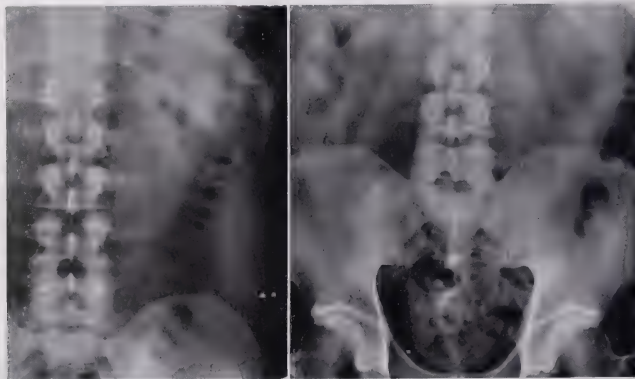


Fig. 184 (left). Supine. The descending colon shows an exquisite haustral pattern. Note the variation in configuration of the individual saccules and in the thicknesses of the haustral septa. Proximally, the longitudinal tenial band completely separates adjacent saccules while distally the saccules communicate with each other.

Fig. 185 (right). Supine. The rectum is distended with small scybalae. The mottled fecal material in the ascending colon and the row of gas collections, some of which enclose scybalae, in the descending colon are typical.

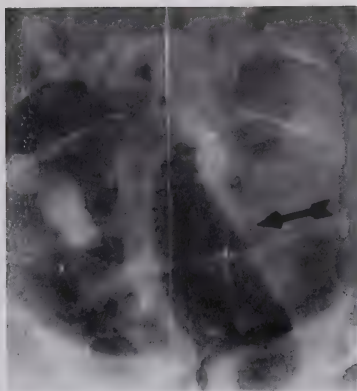


Fig. 186A.

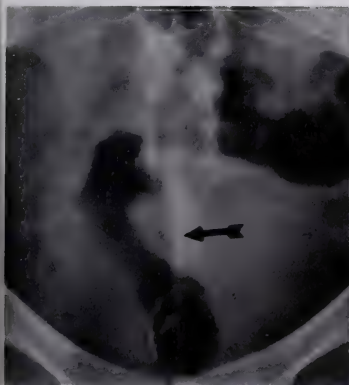


Fig. 186B.

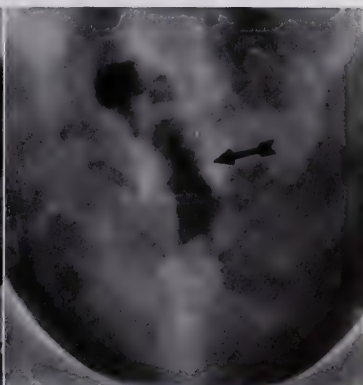


Fig. 186C.

Figs. 186A, B, C. Three different cases showing bizarre configurations of the rectum in the absence of intrinsic or extrinsic lesion.

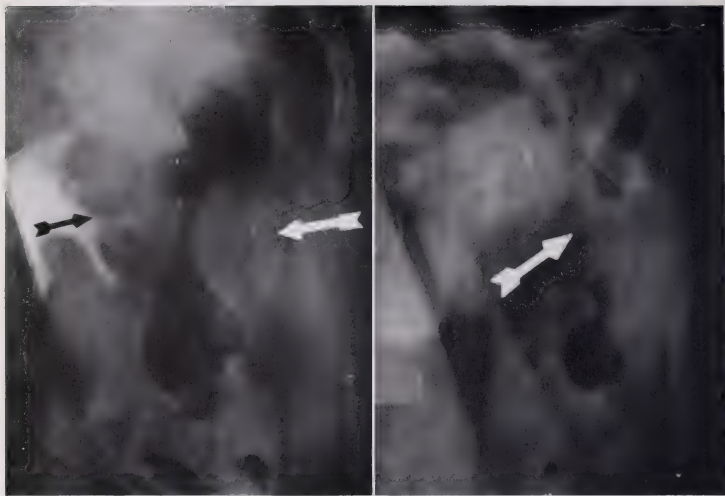


Fig. 187 (*left*). Supine. No intrinsic lesion. A bizarre dumbbell configuration in the proximal descending colon is present. This disappeared on subsequent films. The narrowed channel (between arrows) may be mistaken for a constricting lesion but there are obvious peculiar functional changes on each side of the expanded adjacent portions.

Fig. 188 (*right*). Supine. No intrinsic lesion. Another dumbbell configuration with a narrowed segment (arrow) connecting expanded irregularly shaped regions. This is not a stable configuration. A segmental contraction is occurring in the narrowed region which is displacing gas both proximally and distally and will shortly become complete.

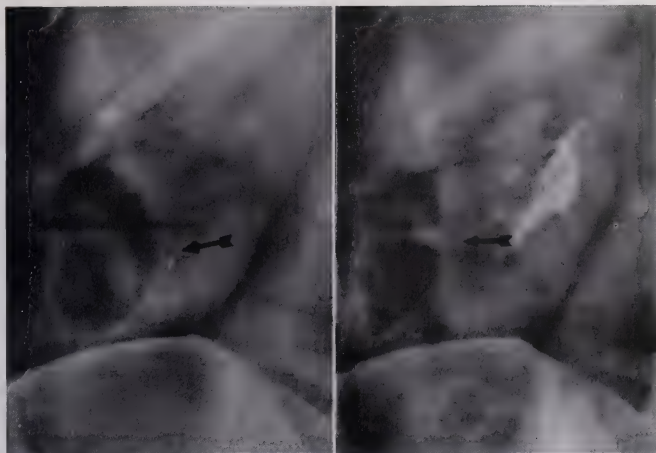


Fig. 189A (left). Supine. No intrinsic lesion. A large discrete bean-shaped collection of gas (arrow) is present on the right side. No other gas is noted in the colon.

Fig. 189B (right). Ten minutes later, during intravenous pyelography, the collection of gas (arrow) is divided into two by a transverse septum.

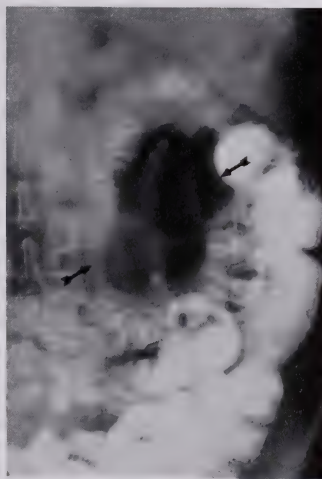


Fig. 190. Supine. A distended, lobulated collection of gas (arrows) is seen in the left upper quadrant distinct from the small bowel. This was demonstrated to be gas trapped at the apex of an elongated sigmoid.

II. CARCINOMA OF THE COLON*

Patients with carcinoma of the colon may present themselves with indefinite complaints such as vague abdominal discomfort, weakness, loss of weight or anemia. As a result, attention may not be immediately focused on the colon and a variety of other roentgen examinations may be requested. Many patients often do not present themselves until complete intestinal obstruction occurs. The roentgen findings indicative of complete mechanical obstruction of the colon are well known and will not be repeated here. However, incomplete intestinal obstruction may be present and go unnoticed clinically because the patient does not complain of constipation and in fact may present with diarrhea. Signs of incomplete obstruction may therefore be discovered accidentally on a film of the abdomen. In several instances, the diagnosis of an obstructing lesion in the region of the hepatic flexure (Fig. 191) has been obvious on oral cholecystography but has been missed because of the fact that attention was confined to the gall bladder. The degree of distension proximal to a partially obstructing lesion may be as great as that present when obstruction becomes complete. However, gas and fecal material may be seen beyond the lesion in portions of colon of normal caliber. Functional changes immediately distal to such a lesion including the persistent presence of gas are not uncommon. The fecal material proximal to a partial obstruction may remain relatively normal in appearance or become quite fluid. Fecal content beyond the site of a partial obstruction may remain fluid but usually sufficient dehydration of the fecal stream occurs distal to the obstruction to produce solid material of relatively normal consistency.

The roentgen findings indicative of obstruction may be considered to be indirect evidence of the presence of a lesion which in most cases turns out to be a carcinoma. For our present purpose, we are interested in the direct signs, that is, those roentgen features which can be seen on a simple film of the abdomen which permit a more exact diagnosis of the location and nature of the lesion. In those instances in which the bowel is dilated proximal to the lesion, there is often sufficient gas to permit visualization of the proximal margin of a filling defect (Figs. 192-194). In some instances, it may be desirable to intentionally position the patient so that gas rises to the edge of the lesion. An irregular, protruding, nodular, soft tissue defect at the distal margin of the gas column is indicative of a neoplasm. Because of the large amount of gas and distension frequently present, it is often necessary to view this region of the film with a bright light in order to recognize the soft tissue densities. The distended bowel immediately proximal to the obstructing lesion often forms pouches which extend distally a short distance around the defect and assist in its recognition.

With incomplete obstruction, gas may be present in the colon both proximal and distal to the lesion. It may therefore be possible to visualize both extremities of the filling defect within the bowel (Figs. 195 & 196). Moreover, the narrowed

* Figures for this section appear on page 239 et seq.

central channel within the constricting lesion may also be evident as a result of stasis of gas (Figs. 195 & 196). Careful observation is often required to observe this narrowed channel because it is ordinarily quite faint. It frequently widens at each end; occasionally only the terminal portions may be seen as triangular indentations in the center of the proximal and distal borders of the filling defect. These findings, that is, a proximal and distal edge with a central narrowed channel, may be evident as a result of local gas retention in the absence of significant obstruction (Fig. 197) because of interference with local contractility. Fecal material is rarely seen at the site of an annular carcinoma. The increased contractility proximal to such a lesion required to move the fecal stream apparently is ordinarily sufficient to propel the contents beyond the narrowed area.

In some patients with an annular type of carcinoma, the most clearecut finding is the narrowed central channel (Figs. 198 & 199) rather than the overhanging edges. This narrowed channel usually has an irregular or angular configuration with hazy indistinct margins. Although the edges of the tumor may not be clearly seen, a soft tissue gap between the narrowed gas column and adjacent portions of the colon is usually evident (Fig. 198). In extreme instances of this type, the narrowed channel may be extraordinarily long (Figs. 200 & 201). These are usually scirrhus types of carcinoma which grow predominantly along the long axis of the bowel.

In contrast to an annular or scirrhus type of carcinoma, a carcinoma of the colon may present as a large, usually irregular, polypoid lesion protruding into the lumen of the bowel (Figs. 202-205). This appearance is more frequent in those portions of the colon that normally have a large caliber such as the right side of the large bowel or the rectum. A polypoid lesion such as this may have a narrow pedicle (Fig. 202) or a broad base (Fig. 203). In other instances, a multilobulated or cauliflower type of appearance may be clearly evident as a result of marked irregularities of the surface indicated by bizarre gas shadows within the filling defect (Fig. 204). In some instances, the apparent polypoid appearance is due to thick nodular projections around the entire circumference of an ulcerated lesion (Fig. 205). A large polypoid tumor may distend the lumen and almost completely obliterate it without producing remarkable obstruction (Figs. 206 & 207). It is easy to mistake a filling defect of this type for fecal content or a fecal impaction.

Another type of carcinoma of the colon is the so-called "saucer" variety which shows irregular elevated edges and a flat or ulcerated center. With continued growth, this type of tumor usually becomes the classical annular or napkin-ring type of lesion. In cases of this type, it may be possible to recognize a soft tissue defect within the course of the colon which shows in its center a rather deep angular or irregular ulceration (Fig. 208). The appearance may resemble a Carman type of carcinoma of the stomach with a "meniscus" sign.

In another type of carcinoma of the colon, the growth of the tumor is predominantly towards the outside of the bowel and into adjacent soft tissues, and obstruction is a late phenomenon. This type of tumor appears to be most common in the descending colon and the splenic flexure. At these sites, retroperitoneal

adherence and extension may be marked. Post-operative local recurrences are often of this nature. While the growth of the tumor outside of the bowel may be symmetrical (Fig. 209), more commonly the tumor grows eccentrically and appears to angulate or compress the bowel lumen (Figs. 210 & 211). The tumor mass that results may be so large that its origin in the bowel is not suspected (Figs. 212 & 213). In most cases, however, an irregular column of gas (Fig. 212) or bizarre bubbles (Fig. 213) indicate communication with the bowel. A stellate gas collection within such a tumor suggests perforation and sinus tract formation. (Fig. 214). In other instances, marked excavation of the tumor may occur and a large ragged cavity filled with mottled fecal material (Fig. 215) may be evident. In rare instances, a large mass in the course of the colon is due to intussusception resulting from a carcinoma (Fig. 216).

The fraction of cases of carcinoma of the colon which can be identified on simple films of the abdomen in the absence of all evidence of obstruction is not likely to be great despite careful study of simple films. In the older age group, however, there should be a high index of suspicion and minimal findings (Fig. 217) should be investigated by barium enema.

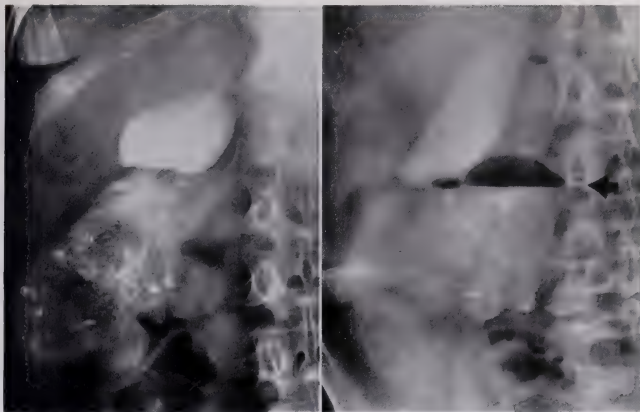


Fig. 191. Oral cholecystography.

Fig. 191A (left). Prone. The gall bladder is well opacified and shows no filling defect. However, of greater significance is the distension of the ascending colon by fluid mixed with retained opaque material. The abrupt termination of this segment in the region of the hepatic flexure indicates an obstructing lesion.

Fig. 191B (right). In the erect position, a long fluid level (arrow) indicates the liquid nature of the contents as well as uniform dilatation of the area. In this case, the distended colon is well demonstrated by retained opaque material but a fluid level such as this, by itself, is sufficient to raise the suspicion of obstruction.

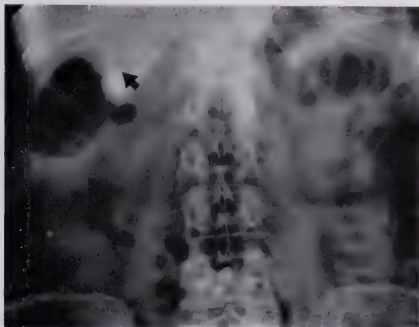


Fig. 192. Supine. Carcinoma of the hepatic flexure. Numerous dilated loops of small bowel containing gas and fluid occupy the abdomen. In the right upper quadrant, gas in the distended hepatic flexure shows an abrupt cut-off with soft tissue projections ("shoulders") into the gas. A centrally located dimple leads into a faintly outlined narrowed channel (arrow) within the obstructing annular carcinoma.



Fig. 193. Prone. Carcinoma of the descending colon. Uniform distension of the proximal descending colon is present. Protruding into the gas column distally is an irregular soft tissue defect (arrow).



Fig. 194. Supine. Carcinoma of splenic flexure. There is a short markedly distended segment in the distal transverse colon. A nodular soft tissue mass (arrow) projects into the wide column of gas.

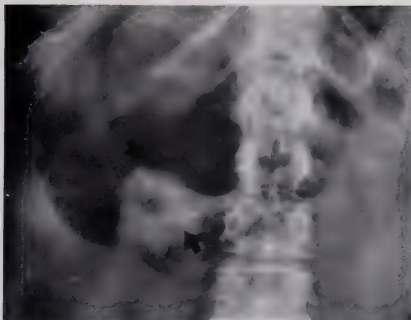


Fig. 195. Supine. Carcinoma of the hepatic flexure. There is marked distension of the hepatic flexure with a mound-like protrusion into the gas column (arrow on right). The transverse colon also contains gas, although it is not distended. As a result, the distal soft tissue protrusions into the lumen are also seen (arrow on left). Moreover, the typical narrow channel in the center of the lesion is well outlined by gas.

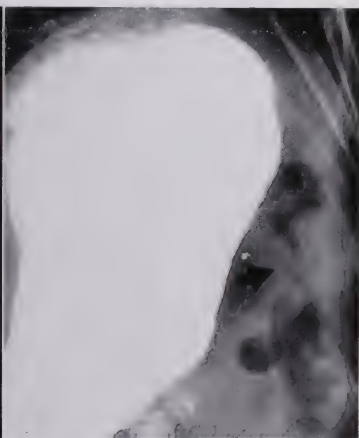


Fig. 196 (left). Prone. Carcinoma of the splenic flexure. Gas is present in the colon on both sides of a markedly narrowed channel (upper arrow). The segment above is irregularly dilated; splenic flexure. The portion below is undistended descending colon with typical haustral pattern. Close examination, particularly under a bright light, shows nodular soft tissue intraluminal protrusions extending into gas, both proximally and distally. To the left of the descending colon is a dilated loop of small bowel (lower arrow) which is in the nature of a "sentinel" loop. (Droplets of mercury are present in the splenic area.)

Fig. 197 (right). Prone. Carcinoma of the descending colon. An eccentric narrowed channel (arrow) is evident in the course of the gas column in the descending colon. Soft tissue "shoulders" project into the gas column at each end. There is no dilatation of the gas-filled segments and no significant obstruction.

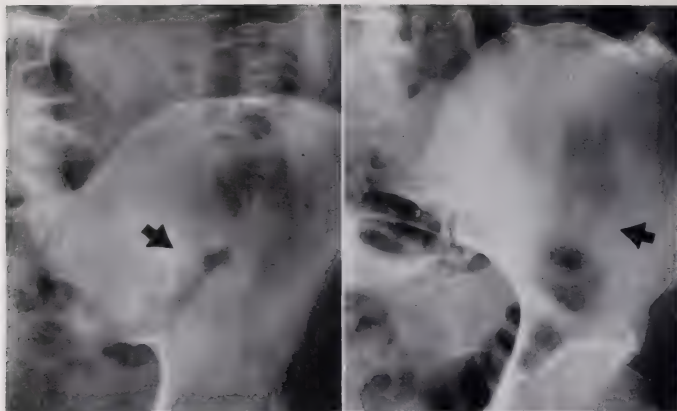


Fig. 198 (*left*). Supine. Carcinoma of the descending colon. A narrow, irregular channel of gas (arrow) is present in the iliac fossa. Overhanging edges are not visible. However, there is a suggestion that the density around the channel is increased and soft tissue gaps are present at each end.

Fig. 199 (*right*). Supine. Carcinoma of the descending colon. A narrow, irregular gas channel is present in the iliac fossa with faintly outlined shoulders proximally. Distally, the channel is overlapped by gas-filled haustrum indicating acute angulation at the junction probably the result of local fixation.



Fig. 200. Prone. Carcinoma of the ascending colon. A long narrowed channel (between arrows) occupies almost the entire ascending colon. The central ulcerated part of this channel is relatively wider than the adjacent portions which show "waisting", i.e. are convex towards the lumen. At the proximal margin of this channel, soft tissue edges are evident. The gas column beyond the lesion is band-like in configuration with irregular contour presumably due to extrinsic involvement. (Large calcified biliary calculi are incidental.)

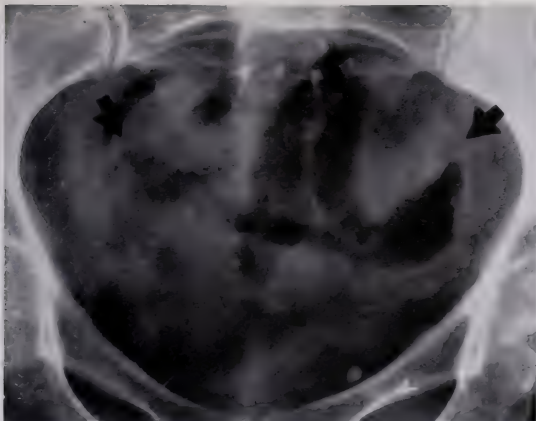


Fig. 201. Supine. Carcinoma of the sigmoid. A long irregular narrow channel (between arrows) with irregularly scalloped walls and no clear proximal or distal demarcation is present in the sigmoid. This is an unusual type of spreading or scirrhous carcinoma.

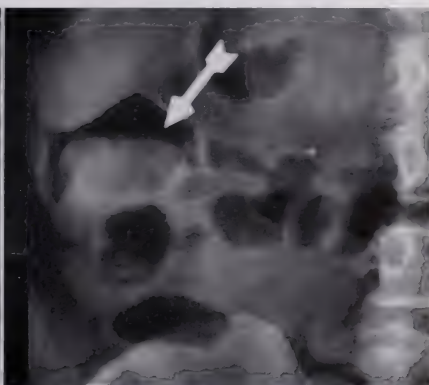


Fig. 202 (left). Prone. Carcinoma of the cecum. The gas-filled caput coli (upper outer arrow) is directed upwards and laterally. A polypoid filling defect (between lower arrows) with narrow pedicle protrudes into the lumen. The density of this defect is not uniform indicating a lobulated or ulcerated surface.

Fig. 203 (right). Prone. Carcinoma of the hepatic flexure. A broad-based filling defect is present in the hepatic flexure. It is eccentric rather than circumferential. There is no obstruction. (The faintly outlined gall bladder indents the colon.)



Fig. 201. Prone. Carcinoma on the ileocecal valve. An irregular, "cauliflower" filling defect (a) is present at the junction of the cecum and ascending colon. Irregular densities and gas shadows within the lesion indicate lobulations or ulcerations.

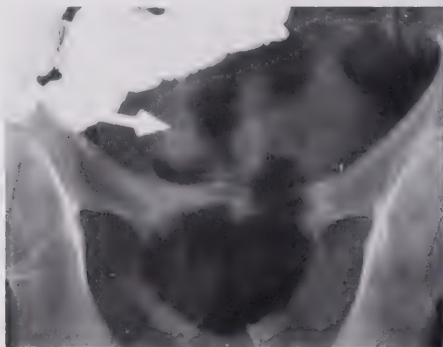


Fig. 205. Prone. Carcinoma of the rectum. The gas column in the proximal rectum is irregularly bordered by multiple soft tissue protrusions which are most obvious along the lateral contours (a) although similar defects are present at each end.



Fig. 206. Supine. Carcinoma of the rectum arising in a large villous adenoma. A huge soft tissue defect (arrow) occupies the lumen of the proximal rectum. The distal margin is partly obscured by mottled contrast material but multiple nodules can be discerned.

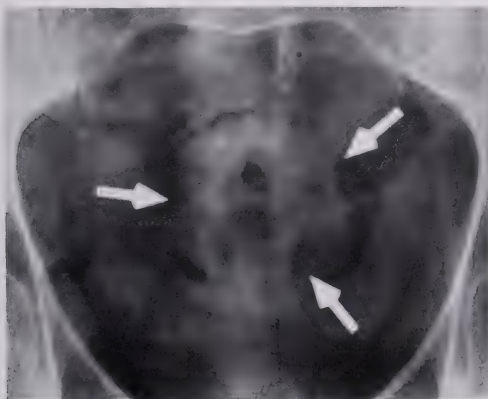


Fig. 207. Supine. Carcinoma of the rectum. A large globular filling defect (arrows) fills the proximal rectum. It is almost completely surrounded by gas except inferiorly. The defect shows numerous ovoid, irregular faint lucencies within its center which do not resemble gas bubbles in fecal material. These result from the irregularly lobulated surface of the neoplasm.

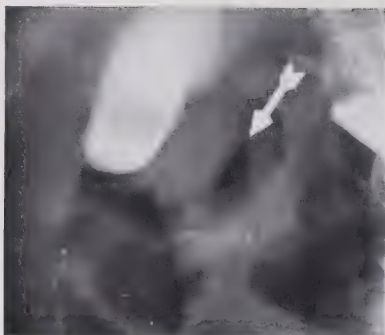


Fig. 208. Ulcerated carcinoma of the hepatic flexure.

Fig. 208A. Oral cholecystography shows good opacification of the gall bladder which contains a single large calculus. However, close observation shows a triangular markedly lucent gas shadow (arrow) in the course of the hepatic flexure. This gas shadow is surrounded by soft tissue densities. In the absence of the central gas shadow, the fact that these soft tissue densities are intraluminal in location would not be appreciated.

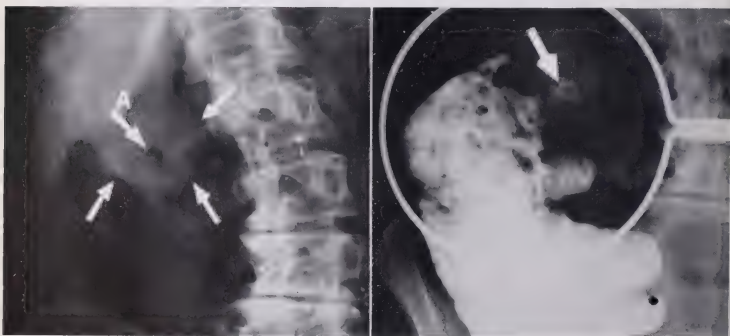


Fig. 208B (left). Prone. Same case—sometime later. The mass in the hepatic flexure (arrows) is not evident as a narrowed channel or a defect outlined by surrounding gas but as a poorly demarcated soft tissue mass in the center of which an angular pocket of gas (arrow A) is trapped.

Fig. 208C (right). Barium administered from above shows no remarkable distention of the ascending colon but there is an abrupt cut-off of the barium column. The small deep central ulceration within the neoplasm is outlined by barium (arrow) and has the same shape seen in Figs. 208A and B.



Fig. 209. Supine. Carcinoma of the descending colon. An elongated soft tissue mass (arrows) is present in the upper portion of the left lumbar gutter. The medial border of this mass is not clearly delineated. The bulging lateral border extends into the retroperitoneal or properitoneal fat (outer arrow). The scalloping of the gas column in the distal descending colon (lower arrow) is easily overlooked. (Large globs of mercury are present in the proximal small bowel.)

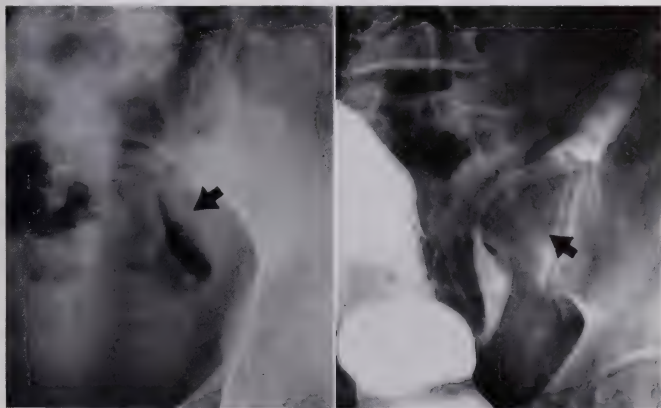


Fig. 210. Carcinoma of the distal descending colon with eccentric extrinsic extension.

Fig. 210A (left). Supine. A thin curved irregular collection of gas (arrow) is present at the brim of the pelvis. Lateral to this collection, there is no clear-cut mass but a uniform increase in density with displacement of loops of bowel superiorly.

Fig. 210B (right). Barium enema shows a large eccentric filling defect. The appearance of the barium-filled residual lumen is identical to the gas shadow seen in Fig. 210A.

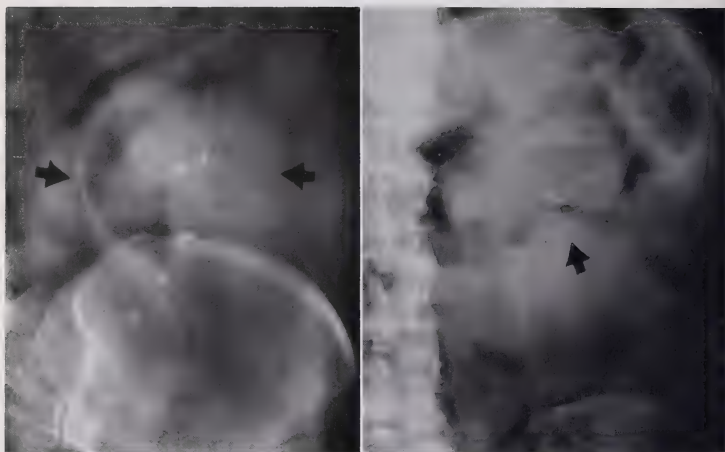


Fig. 211 (left). Supine. Recurrent carcinoma of descending colon. A poorly demarcated globular mass (arrows) is present above the iliac crest. The gas column in the residual lumen of the bowel is arcuate configuration, convex medially. Within the lateral portion of the gas column is a polypoid soft tissue defect which is continuous with the larger mass extending into the peritoneal fat layer. Numerous small bubbles are present in the center of the extrinsic mass. A vertical row of metallic sutures indicates the previous abdominal incision.

Fig. 212 (right). Prone. Perforated carcinoma of the descending colon. A bizarre narrowed irregular gas collection is present in the left upper quadrant. The presence of a mass is indicated by the extensive increased density around the gas collection.

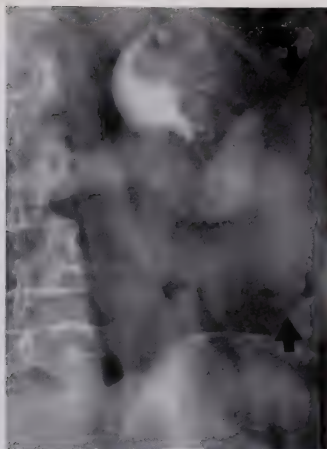


Fig. 213. Supine. Carcinoma of the descending colon. A huge mass (between arrows) is present in the lumbar gutter which is clearly demarcated superiorly and laterally. One would ordinarily not consider a mass of this size to be a primary carcinoma of the colon. There is no evidence of obstruction. However, two small peculiar collections of gas (lower arrow) are present within it which indicate communication with the bowel lumen.

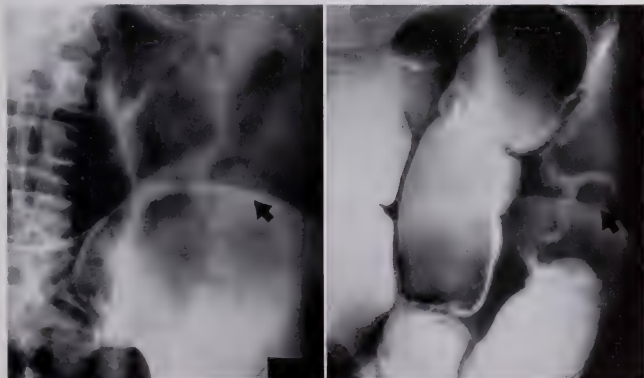


Fig. 214. Perforated carcinoma of descending colon.

Fig. 214A (left). Supine. Faint bizarre or star-shaped collection of gas within a soft tissue density mass (arrow) is present at the crest of the ilium.

Fig. 214B (right). Barium enema shows identical findings (arrow). An elongated loop of sigmoid extends to the left upper quadrant.

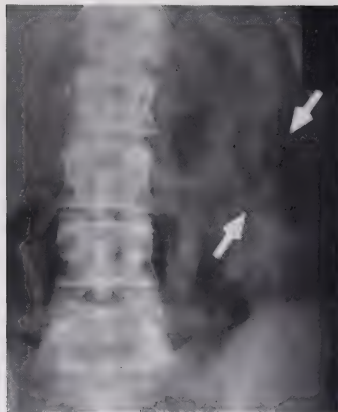


Fig. 215. Excavating carcinoma of the splenic flexure.

Fig. 215A. Supine. Film taken prior to intravenous pyelography shows a large discrete mottled collection (between arrows) of fecal material in the left upper quadrant. This semi-solid (or semi-liquid) material does not take the shape of haustra but has an irregular, angular periphery. It appears to be surrounded by soft tissue densities with no bowel immediately adjacent to it.



Fig. 215B (left). Prone. Film taken several days after 215A. More gas and less fecal material outline a markedly irregular cavity with nodular protrusions into it from all directions (arrows).

Fig. 215C (right). Barium enema demonstrates a large ragged cavity (arrows) which represents an excavated neoplasm. Adjacent small bowel loops are also filled, indicating perforation and fistula formation.

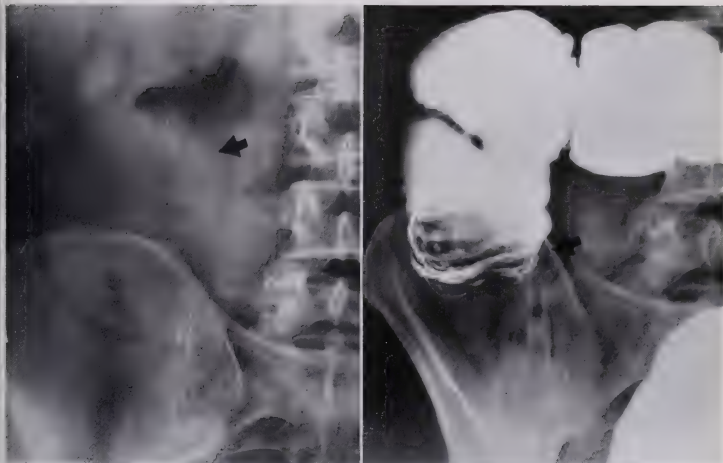


Fig. 216. Intussuscepting carcinoma of the ileocecal region.

Fig. 216A (*left*). Supine. A large globular homogeneous density (arrow) is seen in the usual location of the ascending colon. There is no evidence of obstruction.

Fig. 216B (*right*). Barium enema shows intussusception (arrow). This was due to a carcinoma of the colon arising near the ileocecal valve. The neoplasm *per se* is obscured on both the plain film and the enema by the intussusciens filling the lumen.



Fig. 217. Carcinoma of the ascending colon.

Fig. 217A (*left*). Supine. The haustral pattern of the ascending colon is interrupted by a rectangular gas collection (between arrows). The outer borders of the bowel at this level are well seen at some distance from the gas. The configuration of the gas collection—straight margins and absent septa—is peculiar.

Fig. 217B (*right*). Barium administered from above demonstrates an eccentric filling defect (arrow) in the ascending colon. At operation, a carcinoma was found on one wall.

III. ULCERATIVE COLITIS*

The great value of simple films of the abdomen in the diagnosis of fulminating ulcerative colitis with "toxic dilatation" has been previously described (40 & 41) and will be only briefly mentioned in this section. However, in many patients with less acute or chronic ulcerative colitis, remarkable changes in the gas pattern of the colon are present which are of considerable diagnostic value. In general, the diagnosis of ulcerative colitis on the basis of clinical findings is no great problem and barium enema examination is ordinarily diagnostic. In a limited number of instances, the systemic manifestations such as fever and arthritis may dominate the clinical picture and attention may not be drawn immediately to the colon. In such cases, a film of the abdomen taken for some other purpose may indicate the primary site of disease. An occasional case of asymptomatic or burnt-out ulcerative colitis may be discovered incidentally on a simple film. In some instances, it is desirable to attempt to establish the diagnosis of ulcerative colitis without performing a barium enema, for example, in acutely ill individuals, in children, or during pregnancy. In patients who cannot retain an enema, useful information may be obtained from a simple film.

It is of special interest that simple films of the abdomen may sometimes be more instructive in patients with ulcerative colitis than a barium enema. This arises from the fact that many of the roentgen features result from functional abnormalities which may be obliterated or obscured by uniform filling and maximum distension achieved during the course of a barium enema. Since the most marked changes are present in acute phases of the disease, serial simple films are useful in observing the progress of patients under treatment.

It is characteristic of ulcerative colitis that normal solid fecal material is not present in areas of active disease. When diarrhea is marked, a large amount of homogeneous fluid may be present filling the colon. Some of this fluid must exude from the inflamed surface of the bowel. Moreover, the normal fluid delivered to the colon by the small bowel is not absorbed and is rapidly transported through the colon. In addition to the fluid, there is often considerable gas in the colon. In more chronic cases, the presence of gas is probably a manifestation of a functional abnormality in the motor response of the colon. In acute cases, there may be an increased production of gas within the bowel as a result of bacterial fermentation. In the fulminating variety associated with marked gaseous distension of the colon, much of the gas seems to come from the blood stream since it may persist after ileostomy.

The nature of the functional alterations in patients with ulcerative colitis is not entirely understood but the deviations from normal are quite evident. As pointed out in the section on the normal colon, segmentation of the colon, that is, a division into relatively short compartments, is characteristic of the normal functional state or motor response of the colon. This segmentation is due to a variety of localized contractions which include the thin or mucosal haustral

* Figures for this section appear on page 256 et seq.

septa, the thicker or muscular haustral septa, total haustral contractions as well as contractions of relatively long segments of the colon. This characteristic motor pattern is markedly disturbed in areas involved by ulcerative colitis. None of the characteristic septa or contractions may be present or there may be completely abnormal contractions producing a variety of unusual configurations. Since these configurations do not correspond to any of the normal phenomena, suitable terms are not available and one has to resort to descriptive statements such as "saw-tooth" or "ribbon-like". These phenomena are due not only to abnormal response of the bowel wall to intraluminal pressure changes, but also to a failure to respond normally to the physiological stimuli which integrate and coordinate the activity of the various portions of the colon. They are not simply the result of increased or decreased "tone". Terms such as dyskinesia or dystonia have been coined to refer to this type of behavior. The irregular contractile phenomena are usually associated with abnormalities in caliber which range from the huge distension seen in fulminating ulcerative colitis to marked narrowing which fails to distend even during a barium enema. Narrowed segments which would ordinarily completely collapse may persist indefinitely. As pointed out above, many of these functional abnormalities are obliterated during the course of a barium enema. The only functional changes which may persist after complete filling with barium may be an absence of the normal haustral pattern and a rather uniform limitation in distensibility and extensibility.

In a general way, the most bizarre functional abnormalities are seen during acute phases of the diseases (Figs. 218 & 219). A marked "saw-tooth" appearance may be seen with alternating spikes and indentations into the gas column. This "saw-tooth" pattern may be fine (Fig. 218A) or coarse (Fig. 219). Many of the spikes presumably correspond to areas of ulceration although deep pseudo-diverticular pockets are rarely evident except in the fulminating variety. The indentations produce a scalloping of the contour which can often be traced into the gas column as either thick, irregular septa or flat, pseudo-polypoid protrusions. In some cases, a narrow lumen associated with very coarse scalloping of the borders indicates marked thickening of the bowel wall, presumably the result of hyperemia (Fig. 220). In acute phases, there is frequently a large amount of fluid in the bowel as well as distension of small bowel loops due to a reflex ileus.

In the more chronic stages of ulcerative colitis, the functional changes described above as a "saw-tooth" pattern are not likely to be present. The most prominent finding is usually a simple absence of septation or segmental contractions over a considerable length of the colon. This produces a "ribbon" or band-like pattern when the involved segment has a uniform caliber (Fig. 221). Superimposed on the basic ribbon configuration there may be narrowed, partially contracted, areas of variable width and length intervening between relatively dilated segments (Fig. 222). The caliber of the involved portions of the colon in an inactive stage may be normal, irregularly increased or rather uniformly diminished. In association with the "ribbon" pattern, there is often a surprising lack of evidence of mucosal irregularity such as pseudo-polypoid changes sug-

gesting that there has been extensive mucosal healing. In other instances presumably in individuals with frequent exacerbations or chronically active disease, pseudopolypoid changes may be marked (Fig. 223). In patients who show the ribbon pattern, a shortening or at least a lack of redundancy of the colon is usually present as well.

It is rare on a simple film of the abdomen of a patient with ulcerative colitis to visualize sufficient gas throughout the colon to be able to determine the exact extent of the disease. Nevertheless, in many instances, the most important segment from the point of view of surgical therapy, that is, the rectum, can be observed and the configuration and distensibility of this area determined. It may be possible to recognize, for example, that the rectum is intact and that the disease process is segmental in nature (Fig. 224).

Acute fulminating ulcerative colitis with "toxic dilatation" shows very remarkable distension of segments of the bowel. The segment most commonly involved is the transverse colon which may be hugely distended. The segment next most commonly involved by marked distension is the sigmoid. The descending colon rarely shows as severe distension as the adjacent portions. The bowel is also fixed in position as can be demonstrated when the position of the patient is changed. In areas of less severe involvement, the haustra may persist but are thickened or incomplete while in areas of maximal involvement the haustra completely disappear (Figs. 225 & 226). Deep ulcerations may be seen extending beyond the contour of the colon (Fig. 225). A very prominent feature in many cases is a huge number of pseudo-polypoid projections representing residual islands of markedly inflamed mucosa projecting into the gas column (Fig. 226). Associated with these projections, the wall of the bowel may show a marked scalloping as well as diffuse thickening. In the later stages, these pseudo-polypoid residual islands of epithelium also disappear and the bowel wall may become extraordinarily thin. Perforation is therefore common but in most cases is locally sealed-off and cannot be identified. In a number of instances, the perforation may be free and the presence of gas in the peritoneal cavity recognizable by conventional methods (Fig. 227).

The changes described above in patients with ulcerative colitis of the chronic, acute or fulminating variety are frequently sufficiently characteristic to warrant this diagnosis with little reservation. Clinical confirmation is ordinarily rapidly forthcoming. Occasionally, particularly in elderly individuals, a "ribbon-like" pattern may be seen in the descending colon (Fig. 228) or more severe functional changes may be present as a result of prolonged use of drastic cathartics (42) (Fig. 229). Marked dilatation of the colon occurs in a variety of conditions such as sprue or scleroderma or as a result of a paralytic ileus. Under most circumstances, however, the roentgen features of these conditions can be distinguished from the findings described above in ulcerative colitis. It is likely that specific forms of diffuse colitis may be more difficult to differentiate from nonspecific ulcerative colitis but personal experience with these conditions is limited.



Fig. 218. Subacute nonspecific ulcerative colitis. Fever, bloody diarrhea, abdominal pain and distension for three months. Sigmoidoscopy was negative for six inches; blood was seen coming from above.

Fig. 218A. Supine. The outline of the gas column in the distal transverse colon and sigmoid shows diffuse, fine serration or a "saw-tooth" appearance. Faint nodular soft tissue projections extend into the entire extent of the visualized contours. These represent the congested mucosa with intervening ulceration. The caliber of the bowel is not decreased and filling is continuous without septa or segmentation. Mottled fecal material is present in the ascending colon but no normal fecal material is seen distally. As demonstrated in the next figure, a film taken with the patient prone, the "absent" descending colon and rectum are filled with fluid. One continuous column of fluid and gas fills the entire left side of the colon.



Fig. 218B (left). Prone. Gas and fluid have exchanged positions as compared with Fig. 218A. The ascending colon shows a pattern identical to that seen in the transverse colon and sigmoid. The transverse colon (between upper arrows) is filled with fluid except for a thin irregular column of gas floating in its center. The outer walls of the transverse colon are well delineated by pericolic fat. A similar appearance is seen in the proximal sigmoid (lower arrow). The rectum is normally distensible.

Fig. 218C (right). Supine. Re-examination of the abdomen four days later shows a remarkable change in the appearance in the distal transverse colon. A few thick septa (arrows) separated by distended segments have appeared. The contours are still somewhat irregular with flat scalloping or double borders. Gas and fluid in the descending colon are faintly seen. Normal fecal material extends into the proximal transverse colon. These changes reflected improvement in the clinical status.

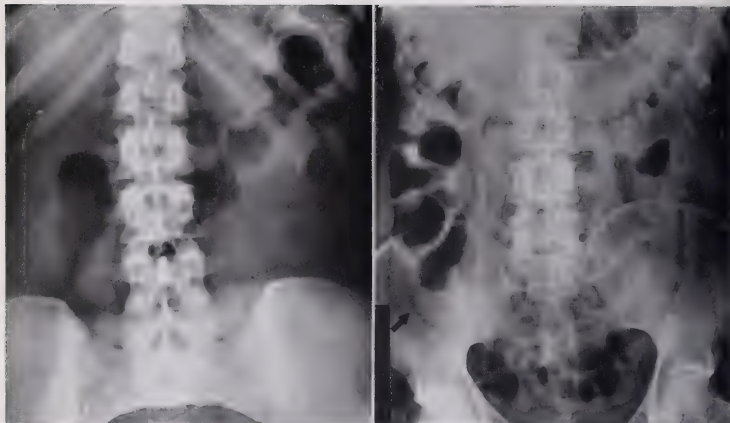


Fig. 219 (left). Supine. Patient with known chronic ulcerative colitis was readmitted for recent exacerbation of diarrhea, fever and abdominal pain. No normal fecal content is present in the colon. The homogeneous densities in the flanks and mid-abdomen suggest dilated fluid-filled loops of bowel. The ascending and transverse colon are outlined by a continuous column of gas which is grossly saw-tooth in outline with total absence of normal segmentation or haustral pattern. The colon is also short.

Fig. 220 (right). Acute nonspecific ulcerative colitis. Twenty-four hour history of bloody diarrhea and lower abdominal pain. Sigmoidoscopy showed congested, edematous, ulcerated mucosa. No specific etiology could be established. Patient responded well to symptomatic therapy over a period of two weeks.

Simple supine film of the abdomen taken shortly after admission. No normal fecal material is present in the colon. The transverse colon shows a markedly coarse, scalloped or "saw-tooth" pattern with thin soft tissue protrusions into the lumen. The basis for this pattern is presumably the normal haustral pattern modified by "spasm" and congestion and edema of the wall. Spasm in the descending colon results in thin continuous gas column with faintly scalloped borders. A row of bubbles lateral to the descending colon (arrows on left) proved to be diverticula on subsequent barium enema examination. Dilated gas-containing loops of small bowel are present in the mid-abdomen. Incidentally, the appendix (arrow on right) also contains gas. Barium enema, two weeks after admission, showed changes of ulcerative colitis from the hepatic flexure to the rectum.

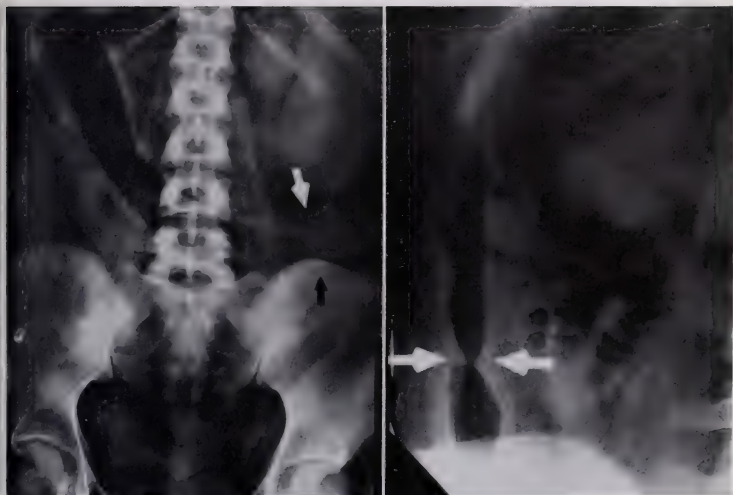


Fig. 221. Chronic ulcerative colitis of 12 years. Because of persistent bloody diarrhea, the patient was admitted for evaluation. Afebrile.

Fig. 221A (left). Supine. No normal fecal material is evident. The entire colon distal to the hepatic flexure is continuously filled with fluid and gas. The junction of the gas column in the transverse colon with the fluid-filled dependent splenic flexure (between arrows) is indicated by the distal tapering of the gas column. There is complete absence of haustral pattern. The bowel has a "ribbon-like" appearance with a rather uniform, fairly wide, caliber. No pseudopolyps are evident.

Fig. 221B (right). Prone film on same patient demonstrates a narrow, short and straight, cecum and ascending colon. The apparent increase in the thickness of the bowel wall is due to the presence of fluid as well as gas. The width of the gas column is therefore deceptive but the other features—lack of haustration, irregularity of the borders, short and straight course—are reliable findings indicative of intrinsic inflammatory disease. The localized indentation (arrows) at the level of the ileocecal valve is also characteristic.



Fig. 222. Chronic ulcerative colitis of two years duration. Diarrhea and abdominal cramps increased in the two months prior to admission.

Prone. No normal fecal material is present. It is likely that there is considerable homogeneous fluid throughout the colon. The gas pattern in the proximal descending colon shows sharp smooth margins with contracted segments of variable length and width between distended areas. This is essentially a "ribbon" pattern with irregular contractility. No pseudopolyps are evident.

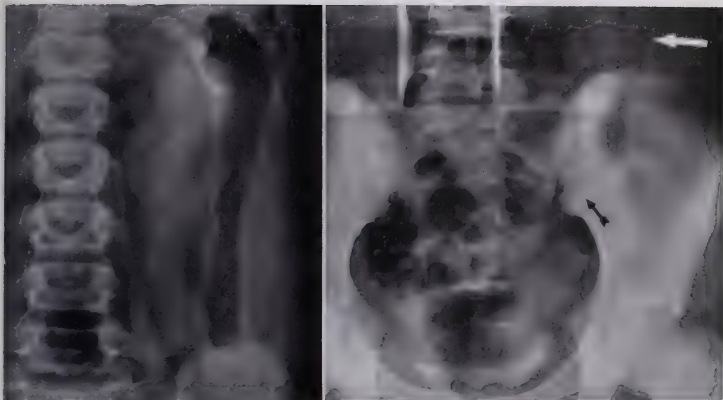


Fig. 223 (*left*). Chronic ulcerative colitis for four years with mild exacerbation.

Prone. No normal fecal material is present on the left side of the colon. The descending colon is continuously filled and of rather uniform caliber. Numerous pseudopolyps are seen along the contours and thin the gas column. The absence of bizarre contractions, serration of the contours and of distended small bowel suggest a "quiet" picture indicating minimal acute disease. (The marked osteoporosis is the result of steroid therapy.)

Fig. 224 (*right*). Chronic "segmental" ulcerative colitis of several months duration in a child. Supine. The transverse colon (arrows) is unusually low in position and shows a ragged outline with thickened wall (lower arrow). The distal portion of the gas column (upper arrow) is narrowed indicating the presence of fluid. The borders of the narrowed gas column are irregular and angular. The rectum shows normal contractibility and normal configuration. (Opaque material in the bladder is part of intravenous urologram.)

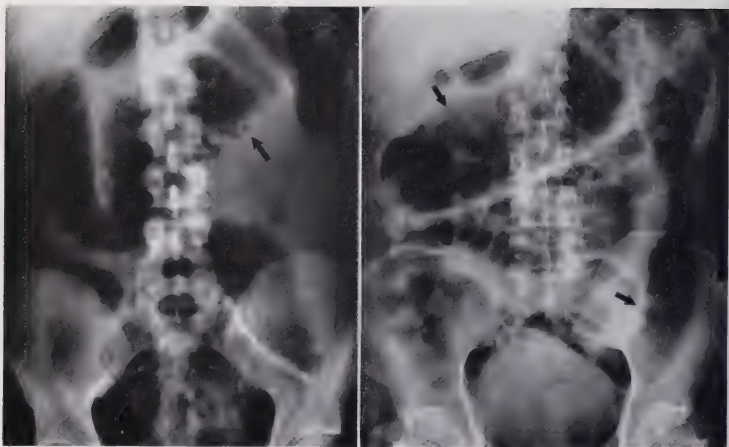


Fig. 225 (left). "Toxic dilatation" during the course of fulminating ulcerative colitis.

Supine. Marked dilatation of the transverse colon and sigmoid with numerous deep ulcerations (arrow) resembling pseudo-diverticula is present. The haustral septa are absent. The borders of the gas colon show numerous irregular, flat and polypoid protrusions. The distended segments of the colon maintain their normal positions and are not elongated. The sigmoid, while distended, has a flaccid appearance. The bowel wall is thickened.

Fig. 226 (right). "Toxic dilatation" during fulminating ulcerative colitis.

Supine. Huge distension of the transverse colon with thickening of the wall and innumerable pseudo-polypoid projections (upper arrow) into the lumen. Similar changes are present in the descending colon (lower arrow) although distension is less marked. Gas-distended loops of small bowel fill the mid-abdomen but have a normal course and configuration. (The bladder is distended and fills the pelvis.)



Fig. 227. Erect. "Toxic dilatation" with free perforation. A large amount of free intraperitoneal gas present below the left leaf of the diaphragm and also trapped over the liver (upper arrow). The descending colon (arrow on left) shows deep ulcerations in profile and markedly thickened septa. Streaks of gas lateral to the descending colon may be retroperitoneal.



Fig. 228. Supine. No intrinsic lesion. "Pseudo" ribbon-like configuration of the descending colon with double contours in places suggests the possibility of chronic ulcerative colitis. Fecal material (arrow) in the lumen simulates a polypoid defect.



Fig. 229. Supine. "Cathartic Colon". No normal fecal material is present. There is continuous filling of the colon with absent haustral pattern and irregular distensibility. No polypoid defects are present. There was a history of daily ingestion of drastic laxatives for many years because of constipation.

IV. MISCELLANEOUS LESIONS OF THE COLON*

In addition to carcinoma of the colon and ulcerative colitis, a variety of conditions can, on occasion, be suspected from changes in the pattern of the colon seen on simple films. Rarely, a small polyp is evident within the gas column as a circumscribed homogeneous filling defect (Fig. 230A & Fig. 230B). The appearance can scarcely be differentiated from a small fecal scybala unless the remainder of the colon is completely clean. A large villous adenoma may however be quite evident on a simple film and may permit the recognition of one cause of uremia (Fig. 230C). It is surprising that diverticula are not seen more often. This is probably due to the fact that diverticula are ordinarily filled with fecal material rather than gas or that small collections of gas seen in the course of the colon are assumed to be within fecal material in the lumen. However, diverticula may become extraordinarily large and can then usually be identified with little difficulty (Fig. 231). Of greater importance is the fact that diverticulitis may be associated with intramural sinus tracts which retain gas and can therefore be recognized on a simple film (Fig. 232-234). In addition to the tract, diverticula in the region are frequently seen as well as an inflammatory mass surrounding the area and displacing adjacent viscera. A large abscess cavity presumably arising from a perforated diverticulum may also be evident by retained gas and fluid (Fig. 235). Occasionally an abscess cavity associated with a perforated carcinoma may show a fistulous tract and simulate diverticulitis (Fig. 236). In the majority of instances of acute diverticulitis, little is to be seen on a film of the abdomen except perhaps an absence of gas shadows from the left iliac fossa associated with a slight ill-defined increase in density of the region and distension of adjacent small bowel.

Secondary changes in the cecum, ascending colon and terminal ileum are frequently seen in patients with acute appendicitis or with an appendiceal abscess (43) (Figs. 237 & 238). A soft tissue "gap" may be seen in the right iliac fossa due to spasm of the bowel in this area or due to an inflammatory mass. Displacement or compression of gas-filled segments of bowel may be evident or adjacent loops of bowel such as the ascending colon may show irregular dilatation (Fig. 237). Discrete dilatation of a portion of the colon in an irregular fashion has a similar significance as a "sentinel" loop of small bowel, that is, it may indicate an adjacent inflammatory process, for example, an acute cholecystitis (Fig. 239). Changes simulating those seen in acute appendicitis may be seen as a result of perforation of a cecal ulcer (Fig. 240) or in association with tuberculosis in this area (Fig. 241).

Infarction of the colon (44) may occur either as a result of mesenteric occlusion or incarceration in a hernia. During repair of a hernia, a compromised portion of the colon may be replaced and fail to recover completely (Fig. 242). A narrowed segment of colon with effaced haustral pattern may then persist and simulate

* Figures for this section appear on page 267 et seq.

ulcerative colitis. A benign stricture of the colon may be the result of infarction or, more commonly, appear as a late complication of ulcerative colitis (Fig. 243).

A variety of masses arising in adjacent viscera may compress portions of the colon. The extrinsic nature of such a mass is usually evident because the indentation is smooth and sharply demarcated and continuous with a soft tissue shadow which extends well beyond the colon (Fig. 244). However, if an extrinsic malignant neoplasm involves the wall of the colon directly or circumferentially (Fig. 245), differential diagnosis may be more difficult.



Fig. 230A (left). Supine. A small soft tissue defect (arrow) is present in the distal descending colon. The proximal margin of the defect is smooth, sharp, and round. The distal margin is not clearly seen. No similar defects or scybalae are apparent.

Fig. 230B (right). Supine. Double contrast portion of barium enema confirms the presence of a polyp (arrow).

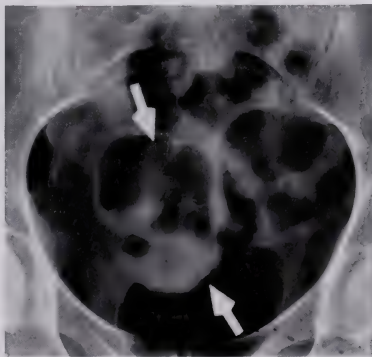


Fig. 230C. Supine. Villous adenoma of the rectum. Simple film of the abdomen shows a large soft tissue protrusion into the gas filling the rectal ampulla (arrows). This does not have the mottled appearance of fecal material and no fecal material is seen in adjacent portions of the bowel. This patient was admitted in stupor and uremia as a result of chronic loss of fluid and electrolytes in the excessive mucus secreted by this tumor. Unfortunately, the mass illustrated was not recognized until barium enema was done subsequently.



Fig. 231. Supine. Diverticula of the sigmoid. Two large diverticula (arrows) are outlined by gas, medial to the descending colon and sigmoid. Diagnosis was proved by barium enema.



Fig. 232. Prone. Chronic sigmoid diverticulitis with intramural sinus tract. A "sausage" shaped mass in the left iliac fossa is indicated by displacement of adjacent loops of small bowel. Within this area, a long narrow column of gas (upper arrows) follows the course of the sigmoid and extends to the rectosigmoid. Proximally, this gas column joins the descending colon eccentrically at its superior margin. A second fainter, interrupted, column of gas parallels the upper one a short distance below it and shows local dilatation (lower arrow) which may be a diverticulum. Barium enema outlined a tract in the wall of the sigmoid identical to the upper gas column, as well as multiple diverticula.



Fig. 233. Supine. Chronic sigmoid diverticulitis with intramural sinus tract. A narrow gas column is present at the brim of the pelvis (lower arrow). Several small circular gas collections (upper arrow) lie above this column and form a row parallel to it. In this case, barium enema showed that the gas column represented the narrowed residual lumen of the sigmoid with multiple diverticula and there was an intramural sinus tract along its superior margin.

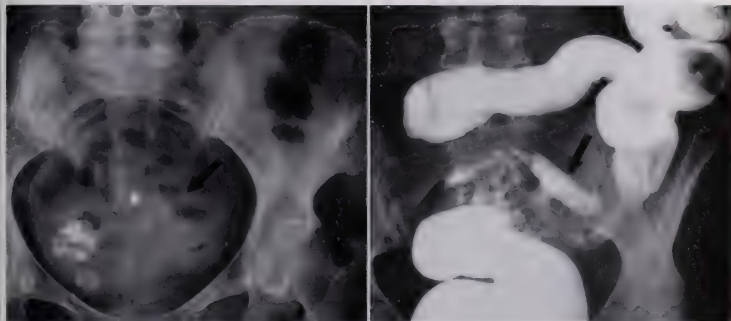


Fig. 234. Chronic sigmoid diverticulitis with intramural abscess or sinus.

Fig. 234A (left). Supine. The left side of the pelvis shows a peculiar collection of gas (arrow) with absence of normal colonic shadows in the region. Several small bubbles are present above and below this gas shadow. The colon proximal to this area is slightly dilated and appears to be cut off abruptly in the iliac fossa.

Fig. 234B (right). Prone. Barium enema shows a wide elongated abscess cavity or sinus tract (arrow) in the superior wall of the sigmoid. The narrowed sigmoid abruptly widens at its junction with the descending colon. Incomplete obstruction was present.

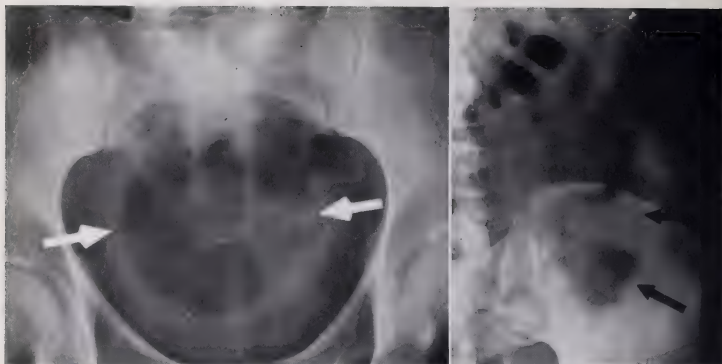


Fig. 235 (left). Supine. Pelvic abscess. A large globular collection of gas is present in the mid-pelvis. The margins of the gas (arrows) are somewhat hazy and, on the left side, irregular. In this latter area there are also several small bubbles. In view of its large size, the lucency of the gas collection is less than would be expected. This is due to the presence of fluid as well as gas in the cavity.

Fig. 236 (right). Supine. Recurrent carcinoma of the colon with fistula to the small bowel. A rounded discrete collection of gas is present in the left iliac fossa (lower arrow). The borders of this collection are somewhat indistinct and irregular soft tissue protrusions extend into it. In addition, a narrow column of gas (upper arrow) continues superiorly and seems to join an irregularly narrowed segment of bowel at the level of the iliac crest.



Fig. 237. Supine. Acute appendicitis, five days duration. The ascending colon (arrow) shows irregular distension with wavy walls and a bizarre inferior contour. A soft tissue "gap" is present in the right iliac fossa. There is considerable distension of both large and small bowel presumably the result of peritonitis.

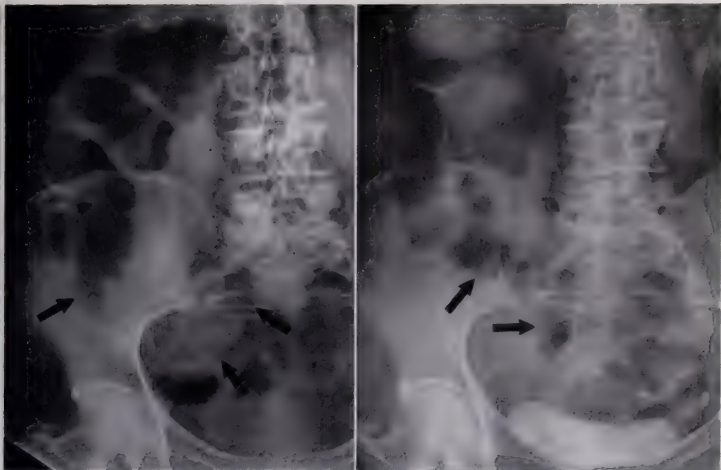


Fig. 238. Acute appendicitis. Appendiceal abscess.

Fig. 238A (left). Supine. There is a suggestion of a soft tissue mass at the brim of the pelvis (arrow) with displacement of bowel laterally. The normal anatomical features of the ileocecal region are distorted. Several small bubbles within the apparent mass suggest matted loops of small bowel containing fluid.

Fig. 238B (right). Supine. Three weeks later. Displacement and indentation of the ileocecal region is evident on its lateral aspect (arrows). An appendiceal abscess was found at exploration.



Fig. 239. Supine. Acute cholecystitis. A portion of the hepatic flexure is distended in a peculiar fashion as a result of "segmental" ileus.

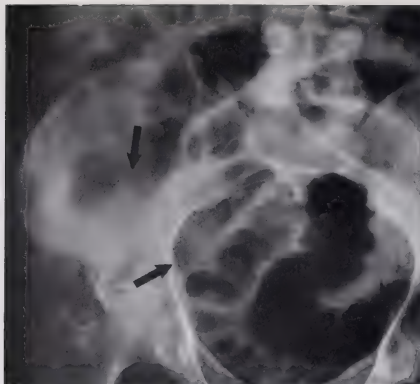


Fig. 240. Supine. Perforated ulcer of the cecum. A soft tissue gap is present at the level of the pelvic brim. Proximally, the distorted cecum shows a double contour (upper arrow). Distally, a faint mottled collection (lower arrow) of fluid and gas is present. An abscess cavity communicating with the cecum was found at exploration. The margins of the opening in the cecum were necrotic.



Fig. 241. Supine. Tuberculous ulceration of the cecum and ascending colon. The cecum and ascending colon appear relatively narrow although this may be due to the presence of an unusually large amount of homogeneous fluid (arrows). A specific diagnosis cannot be made but the appearance is worthy of comment.

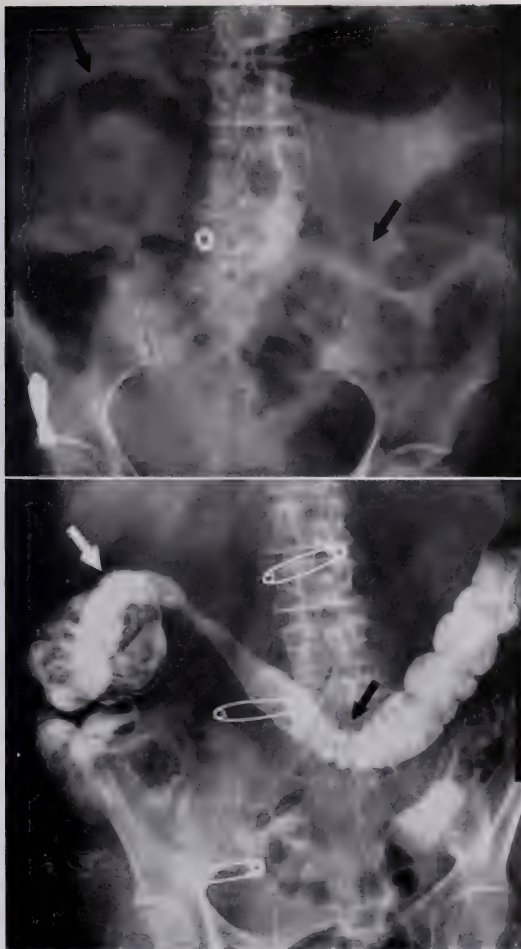


Fig. 242. Segmental infarction of the colon. The patient had a recent repair of an incarcerated ventral hernia. A wound abscess persisted.

Fig. 242A (above). Supine. The transverse colon (between arrows) is straight and narrow with flat flogging of its walls and loss of normal haustral pattern.

Fig. 242B (below). Barium enema shows similar findings. The mucosal and haustral pattern are absent in the narrowed area (between arrows). A short segment immediately distal to the hepatic flexure shows proximal narrowing with tapering of the lumen on each side.

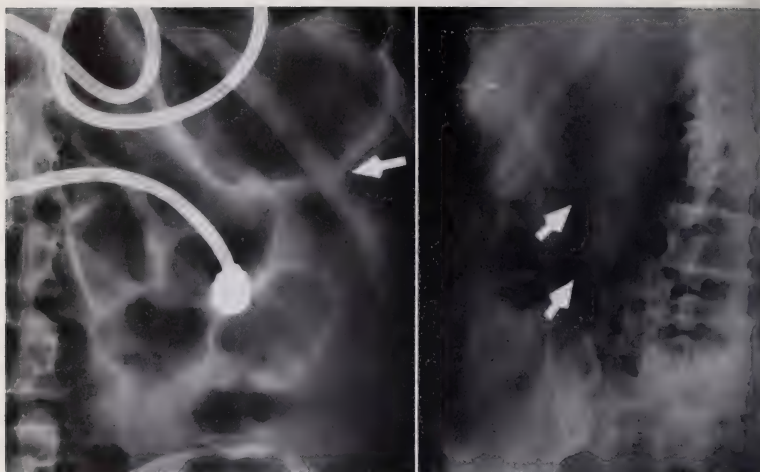


Fig. 243 (left). Supine. Benign stricture in long-standing ulcerative colitis. Incomplete obstruction is present in the proximal descending colon. At the site of obstruction (arrow), instead of soft tissue intrusions into the lumen as seen in carcinoma, the bowel wall bulges distally in a nipple-like fashion.

Fig. 244 (right). Supine. "Courvoisier" gall bladder. There is a sharp arcuate indentation on the superior wall of the hepatic flexure (lower arrow) due to a soft tissue mass. This does not represent the lower pole of the kidney which can be seen at a higher level (upper arrow). Carcinoma of the pancreas was found at exploration.

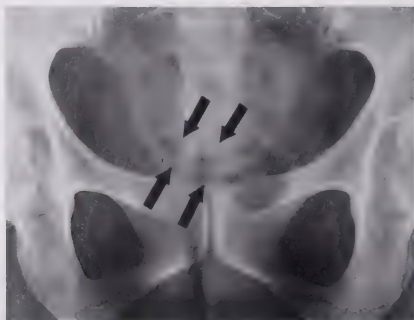


Fig. 245. Rectal shelf due to ovarian carcinoma. The rectum is narrowed as a result of compression on two sides (arrows) with flattening and bulging of the walls into the lumen. The tumor surrounded and invaded the rectum.

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In Memoriam

SAMUEL SILBERT

1894-1959

Dr. Samuel Silbert died on July 10, 1959, at the age of 65. With his passing, The Mount Sinai Hospital has lost a distinguished member who gained international fame in the field of vascular diseases.

Dr. Silbert was born in Raritan, New Jersey on January 24, 1894. He attended Rutgers University from which he graduated in 1912. After receiving his M.D. degree from the College of Physicians and Surgeons of Columbia University in 1917, he spent one year of internship at Lenox Hill Hospital. During World War I, he saw service as first lieutenant in the Medical Corps.

In 1918 he worked with Dr. Charles Frazer of Philadelphia in neurosurgery. As a result of this early training, in 1922 he received an appointment as adjunct in neurosurgery with Dr. Charles Elsberg at The Mount Sinai Hospital. At about the same time he became interested in patients with thromboangiitis obliterans (TAO). In 1924 he established the TAO Clinic at The Mount Sinai Hospital. This was the first Vascular Clinic in New York City and perhaps one of the first of its kind in the world. This Clinic originally established to treat only patients with TAO, was soon to extend its scope and in 1940 changed its name from TAO to that of Peripheral Vascular Clinic.

Dr. Silbert was Chief of that clinic since its founding in 1924. In 1944 he was appointed Associate Surgeon and held that position until his retirement in 1951 when he was appointed Consulting Vascular Surgeon to The Mount Sinai Hospital. He held also an appointment at Montefiore Hospital, first as an Associate Surgeon in 1933, then as Attending Surgeon from 1945 until 1957 when he became Consulting Peripheral Vascular Surgeon.

Dr. Silbert's contributions to the field of peripheral vascular diseases are embodied in many important papers. His experience with TAO dealt with the single largest series of cases in the world. In contrast to the prevailing opinion, Dr. Silbert has shown that TAO is not a progressive disease if patients discontinue the use of tobacco. The causal relationship of tobacco smoking and TAO was one of his major contributions to the understanding and successful management of this once dreaded disease.

Among other of his significant contributions were the use of peripheral nerve sections for the relief of pain due to ulcerative or gangrenous lesions and his advocacy of conservative amputations for gangrene in diabetic and nondiabetic patients alike. In the past few years he undertook a survey of the natural history of patients with arteriosclerotic vascular disease. The cases employed for this investigation were selected from records of his vast private practice. The conclusions of this survey may be of great value to those attempting to assess the results obtained with the use of sympathectomy or vascular grafting procedures.



DR. SAMUEL SILBERT
1894-1959

Dr. Silbert was a dedicated man. His life was almost entirely devoted to this specialty of medicine which he chose early in his career. Attracted by his pioneering accomplishments, many physicians and surgeons from all over the world visited his Clinic to acquire knowledge on a subject which at the time was so little understood. No one failed to be impressed by the sincerity of his convictions or by the integrity of his statements.

His loss will be keenly felt by his associates, colleagues and countless patients who will honor and cherish his memory.

To his dear wife all of us extend our most heartfelt sympathy.

HENRY HAIMOVICI, M.D.,
for the
Editorial Board

IDIOPATHIC PULMONARY HYPERTENSION*

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Whenever one is presented with the problem of diagnosis and treatment of a patient with pulmonary hypertension it is necessary to consider several etiological possibilities. Since the level of pulmonary arterial pressure is a product of pulmonary vascular resistance and volume of flow, increases in either of these factors should theoretically result in an increase in pulmonary arterial pressure. However, inasmuch as the normal pulmonary vascular bed can expand sufficiently to accommodate up to three times the resting systemic flow with little resultant pressure elevation (1), significant, persistent pulmonary arterial hypertension is usually associated with an increased resistance to flow through the pulmonary circuit. Factors increasing the volume of flow through the lungs are of greater importance in accounting for an increase in pulmonary arterial pressure when there is coexisting organic or functional restriction of the pulmonary vascular bed.

DIFFERENTIAL DIAGNOSIS

Table I lists the major causes of chronic pulmonary hypertension, all of which may increase resistance to the flow of blood through the pulmonary circuit and hence increase the pulmonary arterial pressure.

On the arterial side of the circulation, it can be caused by left ventricular failure, mitral valvular disease, left atrial tumors or, more rarely, pulmonary venous obstruction due to congenital "web" formation, and granulomatous or neoplastic involvement.

The clinical pictures produced by this group of lesions can usually, but not always, be distinguished from lesions of the lung parenchyma, lung arterioles or congenital intra or extracardiac shunts which also may result in pulmonary hypertension. These include parenchymatous diseases of the lungs which cause narrowing of the pulmonary vascular bed, such as pulmonary fibrosis associated with sarcoidosis, berylliosis, scleroderma, dermatomyositis, idiopathic fibrosis (Hamman-Rich syndrome), radiation, carcinosis, chronic bronchitis and emphysema and anthracosis or asbestosis. Generally, the history, radiographic findings and pulmonary function studies will help to distinguish this group of lesions.

The pulmonary arterial or arteriolar obstructive lesions caused by multiple pulmonary emboli, periarteritis nodosa, schistosomiasis, sickle cell anemia, neoplastic obstruction, and, rarely, amniotic fluid emboli or cryoglobulinemia also may be responsible for pulmonary hypertension of significant degree.

Within the heart or its adjacent great vessels, interatrial and interventricular

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TABLE I

Causes of Pulmonary Hypertension

- I. Left ventricular failure
 - Mitral valve disease
 - Pulmonary venous obstruction-congenital, granulomatous, neoplastic
 - Myxoma of left atrium
- II. Parenchymal lung disease
 - Sarcoidosis, berylliosis, scleroderma, dermatomyositis
 - Idiopathic fibrosis, radiation, carcinosis
 - Chronic bronchitis and emphysema
 - Anthraxis, asbestosis
- III. Pulmonary arteriolar obstruction
 - Multiple emboli, periarteritis, schistosomiasis
 - Sickle cell anemia, amniotic fluid emboli, cryoglobulinemia
 - Neoplastic obstruction
- IV. Intra or extra-cardiac shunts
 - Inter-atrial, inter-ventricular defects,
 - Patent ductus arteriosus, aortic septal defect
- V. Idiopathic

septal defects as well as patent ductus arteriosus or aortic septal defect may all, in their evolutionary course, be associated with advanced pulmonary hypertension and a clinical picture sometimes difficult to distinguish from idiopathic pulmonary hypertension.

Finally, when all etiological possibilities have been eliminated, there is a definite group of cases which shows marked pulmonary hypertension of unknown cause which has been considered as "idiopathic" ("essential", "primary") pulmonary hypertension. Since this is a diagnosis of exclusion, it is necessary to eliminate the other possibilities before establishing it. For this, cardiac catheterization and some of its ancillary techniques are necessary.

An important determination during right heart catheterization is the level of the pulmonary "capillary" or wedge pressure. If it is accepted that the left atrial pressure is reflected by the wedge pressure, then a normal wedge pressure would eliminate the possibility of mitral stenosis or left ventricular myocardial disease as a cause of pulmonary hypertension and would locate the cause of the hypertension proximal to the pulmonary capillaries. Since mitral stenosis may occasionally present atypical auscultatory findings, if there is any likelihood of its presence and if a wedge pressure is not obtained, it may be necessary to perform left heart catheterization, although it is preferable to avoid such a procedure in patients suspected of having idiopathic pulmonary hypertension.

Right heart catheterization should serve to detect and localize left-to-right and right-to-left shunts. This often assumes importance because the association of pulmonary hypertension with congenital interventricular septal defect, interatrial septal defect, patent ductus arteriosus or aortic septal defect may, in advanced stages, result in either no murmur or atypical murmurs, a loud pulmonary second sound, right ventricular hypertrophy, a prominent main pulmonary artery segment with clear peripheral lung fields, features which cannot be distinguished clinically from those of idiopathic pulmonary hypertension.

However, it has been shown in some cases that the traditional method of detecting shunts by means of comparative oxygen contents in the various chambers may, because of poor mixing, laminar flow of bloodstreams of varying oxygen contents and alterations in the patient's physiological state, fail to reveal the presence of shunts which may be detected by newer, more refined techniques. These include recording of dye dilution curves with sampling from a peripheral artery after injection into the right heart (2); sampling from the right heart after injection into the pulmonary artery (3) (if the newer dye, Cardio-green, is used); sampling from the femoral artery after injection into various sites in the aorta in an effort to localize the site of origin of a left-to-right shunt originating from the aorta (4). Inhalation of nitrous oxide (5), radioactive Kr^{85} (6) or ethyl iodide containing I^{131} (7) with sampling from various sites in the right heart may also help localize the site of entry of a left-to-right shunt. It is preferable that an attempt be made to detect and localize shunts by the newer methods, particularly if balanced shunts are to be eliminated as diagnostic possibilities. It is usually shunts of this type which will be prominent in the differential diagnosis in patients with idiopathic pulmonary hypertension.

Other techniques which may prove helpful in establishing the presence of a shunt include altering the direction of flow through the shunt by increasing pulmonary vascular resistance by inhalation of mixtures low in oxygen, lowering pulmonary vascular resistance by inhalation of 100 per cent oxygen, or diminishing or increasing systemic vascular resistance by the administration of nitrites or norepinephrine. Measures which increase pulmonary vascular resistance or diminish systemic vascular resistance may increase the degree of an existing right-to-left shunt or cause a change in the direction of flow of a previously existing left-to-right shunt. Diminution of pulmonary vascular resistance or increase in systemic vascular resistance will have the opposite effect. However, the danger of sudden alterations in vascular resistance in many of these patients should be realized.

Angiocardiography, if a right-to-left shunt is suspected, or retrograde aortography, if a left-to-right shunt originating from the aorta is present, may be useful in visualizing the abnormality. Simultaneous arterial specimens from the right brachial or radial artery and either femoral artery should also be obtained if there is desaturation in the femoral sample, to rule out the possibility of patent ductus arteriosus with pulmonary hypertension and reversal of flow. In such a situation, the arterial oxygen content is lower in the lower extremities than in the upper extremities.

If all attempts to find a cause for the pulmonary hypertension have been unsuccessful, the patient is considered to have idiopathic pulmonary hypertension.

INCIDENCE

Idiopathic pulmonary hypertension is an entity which has been described with increasing frequency but whether this represents a real increase or simply reflects the increasing number of catheterizations being performed is difficult to

determine. The disease has been described at all age levels, Berthrong (8) reporting several cases in newborns. Yu (9) has recently reviewed the growing literature on this subject and has analyzed 55 cases in patients over 12 years. Although it has been described in infants and in older adults, there is a remarkable predilection for young females in the age range of 20 to 40 years. The female to male ratio in most studies is about four to one. This has led some to postulate that vascular changes in the lung may result from hormonal influences relating to the menstrual cycle or that there may be changes in the uterine vessels with subsequent pulmonary emboli or that the disease in some cases may result from cryptic amniotic fluid emboli. However, there is no direct evidence to support any of these hypotheses and, as mentioned, the disease has been described in both sexes and at all ages.

SYMPTOMS

Table II lists the principal symptoms associated with idiopathic pulmonary hypertension.

Chest pain may resemble that of angina pectoris both in location and in its relationship to exercise. However, it may also have little relationship to exercise. It may be experienced in the right chest or substernally, as well as in the neck. There is no universally accepted explanation for the occurrence of chest pain. Some features suggest angina pectoris and there is evidence to suggest that the available blood supply is insufficient to meet the increased needs of an hypertrophied right ventricle performing increased work. The finding of right ventricular myocardial fibrosis in other forms of right ventricular hypertrophy may well be applicable to the right ventricular hypertrophy of idiopathic pulmonary hypertension (10). Reduction in coronary flow to the right ventricle may result from the diminished cardiac output seen in these patients, with failure to increase normally with exercise, as well as from markedly elevated right ventricular diastolic and systolic pressures, the latter, in some cases, exceeding coronary perfusion pressure. It has been demonstrated in dogs that prolonged right ventricular hypertension may result in a diminution in coronary flow (11). Others have suggested that the distended pulmonary artery may be responsible for the chest pain, and that the pain is unrelated to alterations in coronary flow (12).

Syncope, generally occurring with exertion, is also a common symptom. Two principal explanations have been offered for its occurrence. The investigations of Schwiegk (13), Aviado (14) and Daly (15) have established a reflex mechanism in animals in which an increase in pulmonary arterial pressure is ac-

TABLE II

Symptoms of Idiopathic Pulmonary Hypertension

- Chest pain (dilated PA; "angina")
- Syncope (Reflex; right heart failure)
- Dyspnea and tachypnea
- Generalized weakness
- Hemoptysis; hoarseness (rare)

accompanied by a fall in systemic resistance. This is probably mediated through the vagus as it may be associated with bradycardia. Denervated preparations do not demonstrate this phenomenon. Although the existence of this reflex has not been conclusively demonstrated in man, there have been patients with idiopathic pulmonary hypertension who have had a fall in blood pressure and bradycardia during syncopal episodes (16). Acute right heart failure with further lowering of an already low cardiac output may also cause syncope. Howarth (17) studied a patient with idiopathic pulmonary hypertension during syncope precipitated by exertion and noted a precipitous rise in right ventricular end-diastolic pressure and fall in systemic pressure. It is well known that syncope may frequently occur in other conditions associated with diminution in cardiac output, such as aortic stenosis. The role of impaired coronary flow in producing the syncope in patients with idiopathic pulmonary hypertension has not been fully evaluated.

Dyspnea and tachypnea are most probably related to the excitation of sensory receptors in the pulmonary vascular bed (14). Exercise tolerance is distinctly limited in keeping with the limited capacity to significantly increase cardiac output against the rising pulmonary vascular resistance. Orthopnea, however, is unusual.

Generalized weakness, a frequent and prominent complaint, may also be related to the low cardiac output. The symptoms of weakness and slight dyspnea in a young female may often lead to the erroneous impression of a psychogenic disorder. Such symptoms require careful auscultatory and roentgenographic evaluation if the diagnosis of idiopathic pulmonary hypertension is not to be overlooked.

Hemoptysis and hoarseness, the latter resulting from pressure of the enlarged pulmonary artery on the recurrent laryngeal nerve, may occur, albeit rarely.

CLINICAL FINDINGS

The several clinical findings are listed in Table III. Examination of the patient may reveal neck vein distention with prominent presystolic pulsations in the jugular pulse. The lungs are generally clear and there may be a parasternal heave, evidence of right ventricular hypertrophy. The pulmonic second sound is characteristically markedly accentuated as in other forms of pulmonary hypertension and it is usually split. A systolic ejection sound may be audible in the pulmonic area and a variety of non-specific murmurs may be present. There may be no murmur, or there may be systolic and/or diastolic murmurs of variable

TABLE III

Clinical Findings in Idiopathic Pulmonary Hypertension

80% female (mainly 20-40)

Prominent jugular A-waves

Clear lungs

RVH-Parasternal heave; loud P2

Non-specific systolic and diastolic murmurs or no murmur

Hepatomegaly, jaundice, edema, ascites, clubbing, cyanosis

intensity at the pulmonic area, at the apex, or at the tricuspid area, the latter murmur possibly related to relative tricuspid insufficiency. The soft, diastolic blowing murmur of pulmonic insufficiency, present with pulmonary hypertension from many causes, may be heard and, at times, a rumbling apical diastolic murmur may simulate that of mitral stenosis. Extensive hemodynamic studies relating to the auscultatory findings in idiopathic pulmonary hypertension have not been performed so that the genesis of many of the murmurs is not clear. The rhythm is almost always regular.

The signs of advanced right heart failure, hepatomegaly, peripheral edema, ascites and jaundice, may be prominent, particularly in the later phases of the disease.

Clubbing and cyanosis are also common late manifestations. Cyanosis may be peripheral, due to circulatory stasis related to advanced right heart failure, in which case arterial oxygen saturation is within normal limits, or it may be central, in which instance there is arterial desaturation and secondary polycythemia. The location of the right-to-left shunt in these cases is not always apparent. Cases have been described in which a right-to-left shunt was present during life, the only post-mortem anatomic explanation for which was a patent foramen ovale (18). Extensive bronchial-pulmonary arterial anastomoses, as seen in other forms of pulmonary hypertension, may also be a factor in the production of cyanosis.

LABORATORY FINDINGS

Table IV lists the various laboratory findings. The electrocardiogram demonstrates the non-specific findings of a right ventricular hypertrophy pattern and the peaked P-waves of cor pulmonale. Chest film reveals a large right ventricle and large pulmonary artery but characteristically diminished peripheral pulmonary vasculature. Although these roentgenographic findings are non-specific and may be seen in any form of pulmonary hypertension in which the site of the increased vascular resistance is proximal to the pulmonary "capillaries", the film helps to separate this group of lesions from pulmonary hypertension caused by left ventricular failure, mitral stenosis or parenchymatous pulmonary disease.

Cardiac catheterization studies reveal the expected raised pulmonary arterial pressure and vascular resistance. A further increase in these parameters occurs

TABLE IV

Laboratory Findings in Idiopathic Pulmonary Hypertension

ECG-RVH; RSR; P-pulmonale
Chest X-ray—Large PA; diminished peripheral lung fields
Arterial O ₂ diminished or normal
Polycythemia if hypoxemic
Pulmonary arteriolar resistance elevated
Increase of elevated pulmonary arterial pressure with exercise
"PC" normal; RV diastolic and RA pressures normal or elevated
Cardiac output diminished with failure to increase normally with exercise
Pulmonary function usually normal

with exercise as the pulmonary vascular bed cannot accommodate the increased flow without a rise in pressure. The pulmonary "capillary" pressure is normal. The right ventricular end diastolic pressure and the right atrial pressure are usually elevated in keeping with the presence of right ventricular failure. The cardiac output, low at rest, fails to increase to the normal extent with exercise.

Pulmonary function studies have not been extensively performed but in the few subjects studied, no abnormality was observed (9).

COURSE AND PROGNOSIS

The prognosis is uniformly poor, death usually occurring within two years of the onset of symptoms. Death may occur after prolonged right heart failure or may occur suddenly, possibly related to severe systemic hypotension resulting from one of the reflex mechanisms previously discussed, or to acute diminution of the cardiac output below a critical level or to sudden reduction in coronary flow, possibly associated with an acute rise in right ventricular pressure. During life, these patients are extremely sensitive to procedures which may be well tolerated by others, even with advanced illnesses. Death has been described following barbiturate medication, but whether this is coincidental is difficult to state. Cardiac catheterization has been accompanied by several deaths (16) and it is generally wise to avoid all unnecessary procedures in these patients.

PATHOGENESIS

As the term implies, the pathogenesis of idiopathic pulmonary hypertension is obscure. Pathological examination (Fig. 1) in the great majority of cases demonstrates widespread arterial and arteriolar lesions, including organized thrombi, necrotizing arteritis, medial hypertrophy, intimal thickening and atheromatosis, lesions non-specific in nature which may be found in pulmonary hypertension from any cause, but which are sufficient to account for the raised pulmonary vascular resistance, the outstanding physiological feature of this disease. Occasional cases have been reported without striking pathological changes in the pulmonary arterial tree of sufficient magnitude to explain the marked degree of right ventricular hypertrophy present (19, 20). The crucial question is whether the pathological lesions initiate the hypertension or are a consequence of pulmonary hypertension produced by a functional mechanism, the lesions later acting to sustain and accentuate the increased pulmonary vascular resistance.

In some cases, there is definite suggestion of congenital lesions causing the hypertension as exemplified by infants with evidence of pulmonary hypertension since birth (8) showing lesions suggesting retention of the fetal type of thick-walled, narrow-lumened pulmonary arterioles. There have been reports of a familial incidence of this syndrome (21). In other cases, post-mortem injection techniques have demonstrated aplasia or hypoplasia of the media of the pulmonary arterioles, presumably due to a congenital defect (22).

On the other hand, in favor of an acquired etiology, perhaps with vascular spasm as the initial exciting factor, are: the demonstration that there may occasionally be little pathological evidence in the pulmonary arterial tree to

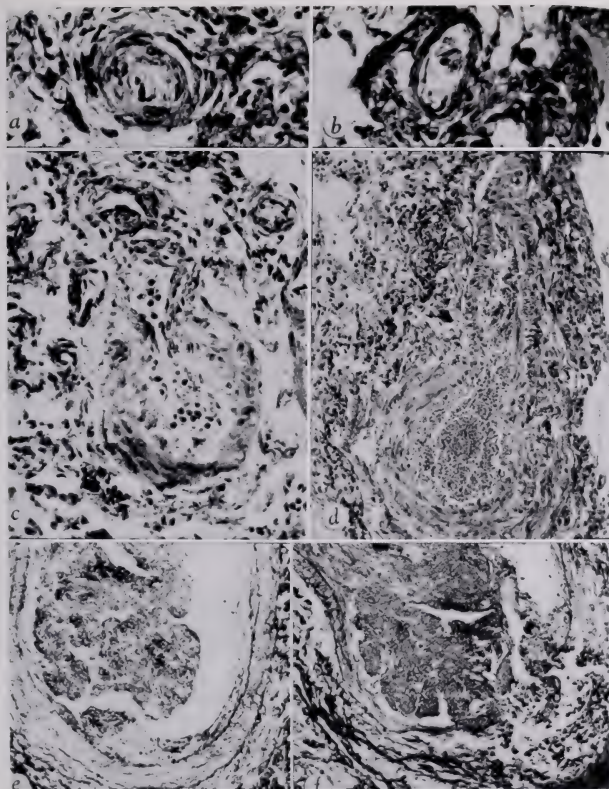


FIG. 1. Anatomic changes in the pulmonary vasculature of a patient with idiopathic pulmonary hypertension.

- a. an arteriole with intimal thickening
- b. same arteriole, but at different level. Wall appears normal.
- c. medial hypertrophy in large muscular artery
- d. normal muscular artery from same patient
- e. thrombus in muscular artery
- f. same artery as in e, at different level, showing focal fibrinoid necrosis of arterial wall associated with thrombus

(Reprinted by permission of British Heart Journal and J. T. Shepherd et al (18).)

account for the observed physiological disturbance; the response, though transient, of some cases to autonomic agents such as tolazoline (23) and acetylcholine (24) with a fall in pulmonary arteriolar resistance, although, in other cases, there has been no response to 100 per cent oxygen inhalation (18); the demonstration that pathological lesions similar to those seen in idiopathic pulmonary hypertension may be produced by acquired, experimental hypertension caused by large left-to-right shunts (25, 26).

Taking the available pathologic evidence and that produced by study of the response of these patients to pharmacologic agents, the consensus is that the increased pulmonary vascular resistance is due mainly to organic factors, although an early, functional vasoconstrictive element may be present.

TREATMENT

The treatment of this condition has been unsatisfactory. Because of the similarity of experimental or an occasional clinical case of multiple pulmonary embolism to idiopathic pulmonary hypertension, some have advocated the use of anticoagulants. The rationale for this appears to be insecure because of the dissimilarity in the age groups of the two diseases and the lack of an adequate history of or cause for the emboli in many cases of idiopathic hypertension. In addition, the advanced arteriolar lesions seen in the majority of cases suggest that it is unlikely that administration of the anticoagulants can reverse the hypertension. There is no good evidence that administration of anticoagulants has materially improved the prognosis in idiopathic pulmonary hypertension.

Others have attempted to approach the problem with the use of autonomic agents. Dresdale reported a fall in pulmonary vascular resistance with tolazoline

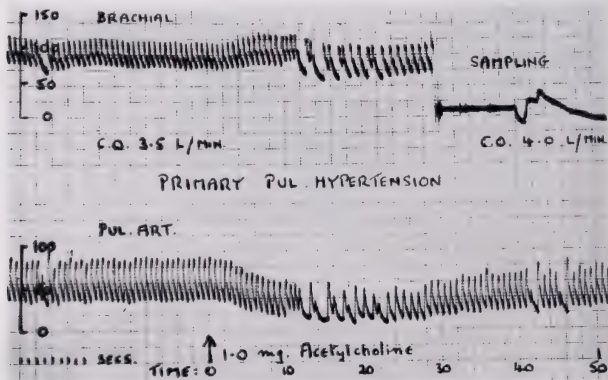


FIG. 2. The effect of acetylcholine injected into the pulmonary artery in a subject with idiopathic pulmonary hypertension. Note the fall in pulmonary arterial pressure and rise in systemic pressure concomitant with a rise in cardiac output. The effect, however, is transient.

(Reprinted by permission of British Heart Journal and P. Wood (24).)

(Priscoline®) injected into the pulmonary artery (23), but these results have not been consistently confirmed by others. Because of the extremely transient physiologic effect of the drug, it could not be used clinically. A similar situation obtains with the use of ganglionic blocking agents such as hexamethonium, which, in addition, causes a pronounced, undesirable fall in systemic pressure. The question that has to be answered when these drugs are employed is whether they reduce pulmonary artery pressure by acting primarily on the pulmonary vasculature or whether they act systemically to reduce pulmonary arterial pressure by reducing pulmonary blood flow. More recently, Harris (27) and Wood (24) have investigated the use of acetylcholine in this condition and have demonstrated a distinct, though transient, fall in pulmonary vascular resistance with a concomitant rise in cardiac output when the drug is injected into the pulmonary artery (Fig. 2).

Although at present the outlook for these patients is grave, it is hoped that further investigation into the physiology of the pulmonary circulation may produce an agent which is sufficiently potent and selective in its affinity for the pulmonary vascular tree so that it may be used prior to the development of irreversible organic lesions.

SUMMARY

The clinical syndrome of idiopathic pulmonary hypertension is described. It is emphasized that this is usually a progressive and fatal disease, having been seen in all age groups but generally affecting young females. Since its clinical features of dyspnea, chest pain, weakness, syncope, variable murmurs, right ventricular hypertrophy and, terminally, cyanosis and right ventricular failure, may often be confused with those of other lesions causing advanced pulmonary hypertension, newer diagnostic methods, utilizing dye dilution curves or inhalation of radioactive gases, are often necessary.

Pathological examination of the pulmonary vascular tree reveals evidence of widespread organic vascular lesions of sufficient magnitude in the great majority of cases to account for the elevated pulmonary vascular resistance. However, an initial functional, vasoconstrictive element may be present. Current attempts at treatment utilize pharmacologic agents which selectively alter the pulmonary vascular resistance, and promising, though transiently effective, results have been recently obtained with acetylcholine injected directly into the pulmonary artery.

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PANCREATITIS IN DISSEMINATED LUPUS ERYTHEMATOSUS

A CASE REPORT

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INTRODUCTION

The etiology of pancreatic inflammatory disease has been the subject of study for many years. The earlier reports were directed towards proving or disproving the validity of the common channel theory of Archibald (1). Recent reviews of the etiology of pancreatitis show better understanding of the pathophysiology of pancreatic disease especially in regard to the factors influencing the onset of inflammation within the organ. Dreiling and Janowitz (2) divided the factors which may play a role in the etiology of pancreatitis into: infectious, mechanical, metabolic and nutritional, vascular, toxic, allergic, traumatic and unclassified. It is well accepted nowadays, however, that the most common etiologies for pancreatic inflammation are alcoholism and gallbladder disease, which account for about 75 per cent of the cases, while the other etiological factors are the cause of 25 per cent of all cases of acute pancreatitis.

Prolonged steroid therapy has been reported as an etiology of pancreatic disease, both experimentally (3-6) and clinically (7, 8). Although steroids have been advocated in the treatment of acute pancreatitis by Rogers *et al* (9) and Kaplan (10), studies by Dreiling *et al* (11) on the effect of these drugs on human pancreatic secretion indicated the possibility of damage to the pancreatic parenchyma resulting from these drugs and cautioned against their use in acute pancreatitis, except in those cases displaying adrenocortical deficiency.

Acute pancreatitis has been reported as a complication of lupus erythematosus (12, 13). The following case report illustrates such a complication in a patient with lupus who had been given prolonged steroid therapy.

CASE REPORT

A 22 year old white female, was first admitted to the medical wards of The Mount Sinai Hospital on July 31, 1952. A diagnosis of lupus erythematosus disseminatus had been made at another hospital in November 1951, following a nine months history of fever and arthralgias, and a one month history of a butterfly rash on her face. She was treated with ACTH and cortisone and discharged. In December 1951, she was rehospitalized for a bleeding duodenal ulcer which was proven by gastrointestinal x-ray examination and successfully treated with ulcer diet. Cortisone therapy was not discontinued. Another admission to the same hospital in July 1952 was necessary because of malaise, fever and a butterfly rash on her face. Despite supportive measures she did not improve and was transferred to The Mount Sinai Hospital for further treatment.

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On physical examination the patient appeared acutely ill. There was a fading facial erythema with faint telangiectasia noted on the face. She had a marked thoraco-lumbar scoliosis. There was slight dullness and diminished breath sounds at the right lung base and a harsh grade III systolic murmur over the pulmonic area. The abdomen was soft and the liver enlarged two centimeters below the right costal margin at the midclavicular line.

Laboratory data showed a hemoglobin of 9.5 gm%, an erythrocytic sedimentation rate of 70 mm/hr, and a white blood cell count of 4,950/mm³, with a shift to the left. The urine disclosed one plus albumin and many white and red blood cells. The urea, fasting blood sugar, electrolytes, serum bilirubin and alkaline phosphatase were normal. The total proteins were 7.6 gm% and the albumin/globulin ratio was 3.3/4.3. Total cholesterol, cholesterol esters and prothrombin time were normal. Coombs test and LE cell preparation were positive. The bleeding and clotting times were normal. Stools guaiac varied from negative to four plus while she was in the hospital. Enteric agglutination tests for typhoid and salmonella were negative. An anti-JK^a (Kidd) antibody was present in a titer of 1:32 to 1:128. Rh and other antibodies were absent. X-ray examination of the dorso-lumbar spine showed marked scoliosis. Chest x-ray was normal. Gastro-intestinal series showed a markedly deformed bulb with evidence of a penetrating ulcer.

The patient was placed under cortisone treatment for two weeks, and then ACTH was prescribed. She was also treated with penicillin and streptomycin. Her fever and arthralgias gradually disappeared after periods of exacerbations and remissions. The ulcer symptoms also subsided with bland diet, antispasmodics and antacids. She was discharged on November 9, 1952.

She had one admission in November 1953 and two more in 1954. Her complaints were fever, arthralgias, abdominal pain and malaise. Her hemoglobin was always low, between 6 and 8 gm%, and controlled with some difficulty with blood transfusions, because of frequent — reactions. Steroids were prescribed intermittently during this period.

The last admission was on October 5, 1954, after a sudden loss of vision that lasted for 20 minutes. She was taken to The Mount Sinai Hospital where a similar episode occurred, followed by a grand mal seizure. The patient also complained of headaches and burning on urination for the past two weeks, but she denied frequency, nocturia or hematuria.

Physical examination revealed a pale, acutely ill, 24 year old white female, with a blood pressure of 180/120, a pulse of 130/min (regular), and a temperature of 97° F. Her physical findings were essentially the same as in previous admissions, with the exception that the butterfly rash was not present. Neurological examination was normal. Urine examination during her hospital stay, showed a specific gravity varying between 1.010 and 1.016, and an albumin 2-4 plus. The erythrocytic sedimentation rate was 138 mm/hr. The blood chemistries disclosed a urea of 62 mg%, a fasting blood sugar of 104 mg%, total proteins 5.7 gm%, albumin/globulin ratio 2.6/3.1, calcium 8.5 mg%, phosphorus 4.9 mg%, creatinine 8.5 mg%. Stool guaiac reaction was negative. The remainder of the laboratory tests were negative.

During the first 24 hours in the hospital, the patient had four grand mal seizures. She was started on intensive steroid therapy, 25 mg of cortisone every six hours, by mouth and 100 mg of hydrocortisone intravenously, daily. She was also treated with dilantin, nembutal and antibiotics. The seizures subsided, but she still complained of headaches. During the first hospital week, the blood urea nitrogen rose to 87 mg%. On the third hospital week she developed abdominal pain and distention, nausea and vomiting.

The blood chemistries were, at this time: urea 232 mg%, creatinine 7.7 mg%, HCO³ 14 mEq/l, chlorides 83 mEq/l, sodium 145 mEq/l, bilirubin 0.23 mg%. The hemoglobin, which had been 8.5 gm% on admission, fell progressively to 5.6 gm%. A monilia infection of the mouth and pharynx became troublesome. During the entire hospitalization she was stuporous. The urinary output averaged 1000 cubic centimeters a day. She became comatose during the last three days, developing finally nuchal rigidity and a tense abdomen with muscular guarding in all quadrants. The patient ceased on the 36th hospital day, in coma.

Post-mortem examination (#12621) showed the emaciated body of a 24 year old white female. Moniliasis with ulcerations was present in the mouth, pharynx and larynx.

The thoracic cavity presented both pleural cavities obliterated by fibrous adhesions that could be easily separated. The lungs disclosed several areas of broncho-pneumonia and microscopically several monilia abscesses.

The pericardial sac contained 400 cc of sanguineous fluid. The heart on microscopic examination disclosed slight perivascular fibrosis and some fibrinoid degenerations of collagen fibers.

There was 1 liter of blood tinged fluid in the abdominal cavity. The gastrointestinal tract showed a hemorrhagic mucosa on the lower two thirds of the esophagus, with ulcerations, chronic inflammation and fungi, microscopically. The duodenum had a small, shallow ulceration, covered by thin mucosa. The liver had an accentuated lobular pattern, with congestion of central lobular areas. Microscopically, there was marked fatty metamorphosis and moderate central congestion.

Grossly, the anterior surface of the pancreas showed areas of fat necrosis and the serosa was congested, dull, and had a mottled greenish tan color. The organ was swollen, and, on section, there were numerous areas dark red in color and well demarcated from the surrounding tissue. The parenchyma was heavily bile stained, congested, but areas of unaffected pancreatic tissue were still present. The pancreatic ducts were unobstructed, and the larger pancreatic arteries showed no occlusion. Microscopically there were large areas of necrosis with much cellular debris and polymorphonuclear cells. Thrombi were present in many veins, both in, and adjacent to necrotic centers. The acini were dilated and filled with inspissated material. The island of Langerhans were unremarkable. Many areas of fat necrosis were present.

The kidneys showed the typical changes of lupus erythematosus, with loop necrosis, "wire loop" changes, and hyalinized glomeruli. Increased amount of fibrous tissue was present. Hematoxylin bodies were seen in some glomeruli and blood vessel walls. The urinary bladder disclosed macro- and microscopic signs of acute and chronic cystitis. Examination of the brain revealed vasculitis, meningitis and encephalitis due to candida albicans. There was also bilateral encephalomalacia present.

DISCUSSION

Although acute pancreatitis has been documented by Brown *et al* (13) as one of the gastrointestinal complications of lupus erythematosus, the mechanism of pathogenesis is far from clear. The possible etiologic factors in lupus include the allergic phenomena (14), auto-immune reactions (15), and acute vascular inflammations (16) that comprise the pathophysiology of florid lupus. Terminally, cardiac and renal involvement may induce the focal necrotic lesions within the pancreas which have been described in the diabetic, the aged, and patients dying from coronary occlusion (17-19). Here, the pathogenetic factor is cardiovascular insufficiency (20).

The necessity for prolonged steroid therapy in the treatment of lupus has added another possible etiology for the occurrence of acute pancreatitis as a complication. Here, too, the mechanism is somewhat obscure. The experimental evidence linking steroids with pancreatitis includes Selye's (4) observations that the styromycin-aminonucleoside-induced pancreatitis of the rat is markedly aggravated by steroids. Stumpf *et al* (3) and Benscome and Lazarus (5) produced pancreatitis in rabbits by cortisone injection. The lesion was acinar in nature with diffuse ductular proliferation and acinar necrosis. Lazarus and Benscome (6) in another study, noted that the early pancreatic lesion occurring in cortisone-treated rabbits was pancreatic ductular proliferation and that this was reversible.

The clinical evidence implicating the steroids in the production of pancreatitis

is discussed in a review of 16 patients with cortisone-induced pancreatitis (7). Carone and Liebow (7) reported the necropsy findings in this series. The most prominent pathologic feature was ectasia of pancreatic acini, together with peripancreatic fat necrosis. Either edematous or hemorrhagic pancreatitis was found in these patients. Included within this series was one patient with lupus.

The only clue to the mechanism whereby steroids may damage the pancreas was suggested by Dreiling *et al* (11) whose studies revealed that cortisone altered the electrolyte secretion of the pancreas in normal subjects towards that observed in patients with chronic pancreatitis. This suggests interference with tubular function and appears to be related to the ductular proliferation observed in the experimental animal and in postmortem cases.

While it is impossible to state with certainty which of the factors was responsible for the acute pancreatitis in the case reported, the occurrence of pancreatitis as a complication of lupus must be stressed. Awareness of this possibility may help further document whether or not prolonged steroid therapy will increase its incidence.

SUMMARY

A case of disseminated lupus erythematosus with extensive pancreatic inflammation discovered at postmortem has been presented. The factors operating in the pathogenesis of pancreatic inflammation in lupus and particularly steroid treated lupus are discussed.

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TWENTY YEARS EXPERIENCE WITH CARCINOMA OF THE BREAST ON WARD SERVICE

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Carcinoma of the breast and its treatment have occupied the thoughts and the pens of physicians and surgeons since the first recorded description of the disease in the "Edwin Smith Papyrus" written about 3,500 years ago. For the greater part of the time, until 1890, it is doubtful whether a single case was cured by the myriad of techniques that were tried. The lesion seemed so inviting to the surgeon—a localized lump or ulcer waiting to be excised or cauterized. Nevertheless, these procedures were invariably followed by local recurrence or generalized dissemination and death.

In 1894, Halsted in Baltimore and Willy Meyer in New York both independently described the operation of radical mastectomy including axillary dissection and excision of the pectoral muscles. In the 65 years since then, this procedure has been evaluated by reports of the survival statistics following the operation as performed in many of the major hospitals in the world. The results while similar have varied somewhat. In all series, the survival rates have improved from decade to decade. Halsted in reviewing the literature prior to 1897, concluded that until that time no woman with carcinoma of the breast had ever been cured (1). In the next decade, five year survival rates of the order of 15 per cent were noted. The rates progressively improved so that in recent series, where all new cases applying are included, rates of about 40-50 per cent are reported (2-8).

NATURE OF PRESENT SERIES

The series of patients to be reported in this communication was reviewed to evaluate the results of treatment on the ward service of a large urban general hospital in which there was no particular emphasis on the treatment of this disease. The series is of additional interest in that some patients were given preoperative radiotherapy, others postoperative radiotherapy and a small number were treated primarily by radiotherapy. As will be noted later, a substantial number of the patients were first admitted for symptoms due to other diseases or to metastases. The existence of a large neurological service was responsible for several patients whose primary symptoms were those of a brain tumor found to be due to cerebral metastases. The sample is not representative

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of a total population but rather of the disease as it exists in the more depressed elements of a large cosmopolitan urban population.

The series consists of all patients who were noted to have a carcinoma of the breast while a patient in the hospital whether or not this lesion was responsible for their admission or was treated. From this group more detailed analysis was applied to those who were treated in any way for their primary disease. No attempt had been made to follow patients with diffuse systemic metastases on admission and it is assumed that all of them died within five years after admission.

Patients who were only seen in the Out Patient Department are not included because detailed records of these patients were not preserved. However, the admission policy of the hospital was very liberal and the only exclusions on this basis would be patients with obvious far advanced disease or those treated elsewhere prior to consultation at the hospital.

TREATMENT POLICY

During the period under review, the treatment policy was a liberal one. The prevailing surgical philosophy was that no patient with a fatal disease should be deprived of a chance for cure if the operation could be accomplished without undue immediate risk. Patients without definite evidence of involvement beyond the operative field were treated by mastectomy. Radical mastectomy was the operation of choice but simple mastectomy was used for elderly and poor risk patients. Simple mastectomy was also used as a palliative operation at times to remove a necrotic or fungating tumor. Policy regarding radiation therapy varied. Preoperative and postoperative treatment were both tried. Preoperative treatment, when used, was given without regard to the clinical stage of the disease. Postoperative therapy, at times, was given on a routine basis but was also used at other times electively for patients with pathological evidence of axillary node involvement. From 1933 to 1940 a group of patients with operable disease were treated electively by radiotherapy. Many of these later had radical mastectomies and are included in the group with preoperative radiotherapy.

The operations with a few exceptions were performed by members of the house staff, by residents in their second, third or fourth year of surgical training. The remaining cases were operated upon by junior members of the attending staff. The techniques displayed substantial variability. The Stewart transverse incision was preferred and primary wound closure without graft was the rule. Four per cent of the patients had skin grafts at the time of mastectomy. In this regard it is important to note that most of the patients had large pendulous breasts so that with a transverse incision, such closure was feasible even after substantial skin excision.

Preoperative x-ray therapy consisted of 120 to 200 KV radiation administered to two, three or four tangential fields to the breast with 1500 to 2400 r to each field, for a total tumor dose of 4500 r in 30 days. To this was added 2400 r to the axilla and to the supraclavicular regions.

Postoperative x-ray therapy consisted of 2400 r to the axilla and supraclavicular regions and 1800 r to the chest wall.

FOLLOW-UP

The patients were followed by periodic visits to a follow-up clinic staffed by members of the surgical and radiotherapy services. Losses were minimal until the war years and thereafter when the character of the population living in the neighborhood of the hospital changed rapidly. This change coupled with difficulties in postal communication at the time caused a 11.5 per cent incidence of untraceable losses in the series. Many of those so lost moved to other cities and some to other countries; others to some other area of the city. Since the population treated was predominantly indigent a good many did not have telephones and moving without a forwarding address made further follow-up impossible.

RESULTS

The series consisted of all cases of carcinoma of the breast admitted to the ward service of The Mount Sinai Hospital during the years 1932 to 1951. There were 3 men and 540 women. Twenty-nine of these patients had been previously treated elsewhere and 514 had not been previously treated.

The overall survival figures are shown in Table I. The series includes 56 cases with obvious distant metastases of whom 22 were admitted for symptoms from the systemic metastases. 388 patients (75.5%) were treated by radical mastectomy. Of these, 73 had preoperative radiotherapy and 188 postoperative radiotherapy. Forty-two were treated primarily by simple mastectomy and 25 of

TABLE I
Cancer of the Breast
5 Year End Results: Ward Service, The Mount Sinai Hospital 1930-1951

	Cases	% of 514	% of 433 (Determinate Cases)
Cases previously treated.....	29		
Cases not previously treated..	514		
Refused treatment.....	11	2.2	
Untraced for full 5 years without recurrence at last examination.....	35	6.8	
Dead within 5 years of other causes without recurrence of cancer.....	11	2.2	
Untraced with cancer at last examination.....	24	4.7	
Dead: Cancer present or presence of cancer unknown.....	223	43.4	51.5
Living with cancer present.....	33	6.4	7.6
Living, free of cancer at 5 years.....	177	34.4	40.9

This series included 56 cases, obviously inoperable, 22 of whom were admitted for symptoms from systemic metastases.

388 patients (75.5%) were treated by radical mastectomy.

42 patients were treated by simple mastectomy.

17 patients with inoperable disease, were treated by radiotherapy primarily.

them received supplemental radiotherapy. Seventeen were treated by radiotherapy alone and 11 refused treatment.

The absolute five year survival rate for the entire series considering all cases lost to follow-up as dead of the disease is 40.8 per cent. The corresponding absolute clinical five year cure rate for those with no clinical evidence of recurrent disease at five years is 34.4 per cent. For comparison with series in which results are reported for traced cases only, survival rates have also been calculated excluding cases refusing treatment and those lost to follow-up. The relative five year survival rate on this basis is 51.5 per cent and the five year relative clinical cure rate 40.9 per cent.

The rate of 40.8 per cent should be compared with the rate of 40.4 per cent as calculated by Rosahn (6) from a large number of series from the literature. As he states, "7 of 11 different reporters present absolute survival rates ranging between the narrow limits of 40.2 per cent and 42.9 per cent. Three reporters, two of whom were from England, gave lower rates—but one, a higher rate."

Age Distribution

The age distribution and the five year survival rates for each decade are shown in Table II and Figure 1. Values are given for the total sample and for those treated by radical mastectomy. When all cases are considered, the five year survival rate is found to decrease with increasing age. The rate remains relatively constant until the 8th decade and then decreases rapidly. The increase at this age level is partially accounted for by general increased mortality over the age of 70. In the treated sample the variations with age are irregular and are within the limits of chance variation, the highest and lowest rates apply to very small samples.

Site

The distribution of the cases by site is shown in Table III. 44 per cent of all the lesions are located in the upper outer quadrant of the breast. The medial

TABLE II
Age Distribution and 5 Year Survival by Age Group

Age Group	Total	Total Series		Radical Mastectomy		
		Survived	% Survival	Total	Survived	% Survival
21-30	7	3	43	3	2	67
31-40	68	28	41	56	28	50
41-50	160	71	44	129	66	51
51-60	150	60	40	117	56	48
61-70	88	39	44	62	37	60
71-80	31	10	32	15	5	33
81-90	4	1	25	3	0	0
Unknown	6	0	0	3	0	0
Total	514	212	41	388	195	50

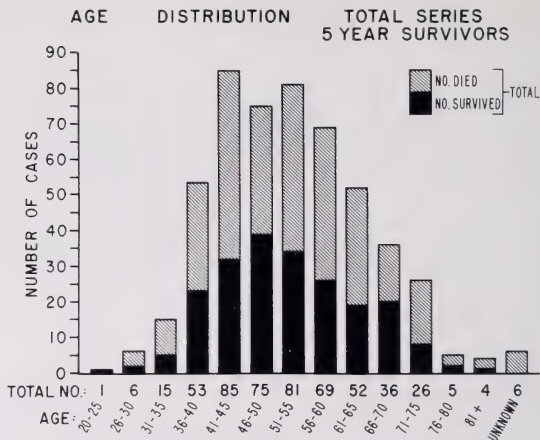


FIG. 1. Age distribution and mortality.

TABLE III
Influence of Location of Lesion on Prognosis

	Total Series (Excluding Cases Referred for Metastatic Disease)				Patients Treated by Radical Mastectomy			
	* No.	% Survived	Survived 5 years	% Survival	* No.	% Survived	Survived 5 years	% Survival
<i>Left</i>	248	49.6	104	42	197	50.8	96	48.7
<i>Right</i>	244	50.4	108	43.5	191	49.2	99	51.8
Center.....	144	29	54	37	100	26	47	47
Upper outer quadrant.....	215	44	97	45	184	47	93	50
Lower outer quadrant.....	64	13	28	44	52	13	27	52
Upper inner quadrant.....	45	9	23	51	35	9	19	54
Lower inner quadrant.....	15	3	6	40	11	3	5	45
Unspecified.....	9	2	4	44	6	2	4	67
Total.....	492	100	212		388	100	195	

hemisphere accounts for but 12 per cent of the cases. Prognosis is worse for centrally placed and lower inner quadrant lesions.

The influence of the duration of disease to admission upon survival is shown in Table IV. The percentage inoperable increases with duration and the percentage survival decreases. The decrease in the latter figure is not as pronounced as might be expected *a priori* since mere survival for prolonged periods with

TABLE IV
Duration of Disease Prior to Admission

Duration	Total		Survivals *	% Survival		Inoperable *	% Inoperable	
	A*	B*		A*	B*		A*	B*
1 month.....	149	148	78	52	53	7	5	5
1-3 months.....	94	91	37	39	41	8	9	9
4-7 months.....	98	92	37	39	40	8	8	9
8-12 months.....	29	28	10	35	36	5	17	18
12-24 months.....	82	78	31	38	40	10	12	13
24-48 months.....	40	36	12	30	33	4	10	11
48 plus.....	22	19	7	32	37	0	0	0

* A—Total series.

* B—Excluding cases admitted for metastases.

untreated carcinoma selects less aggressive malignancies. Indeed some published series even show a reversal of the survival trend with prolonged duration of disease due to this factor (8). The reversal is demonstrated in the inoperability rate in this series which decreases for duration of disease of over 12 months.

TREATMENT

Some form of treatment with hope of arresting the disease was given to 447 patients. Radical mastectomy was the primary modality for 388 patients and of this group 73 received preoperative x-ray therapy, 188 postoperative x-ray therapy and 127 no x-ray therapy.

Simple mastectomy was used for 42 patients and x-ray therapy was elected as the primary modality in operable cases for 17 patients. The gross five year survival rates for these modalities is shown in Table V. Radical mastectomy is shown to be the treatment of choice, with a minimum five year survival rate of 50 per cent and a maximum five year survival rate of 55 per cent if patients lost to follow-up are considered as surviving. In evaluating these results, one must consider the fact that simple mastectomy was generally reserved for poor risk and elderly patients. A five year survival rate of 30 per cent under these circumstances is quite comparable with the rate for more extensive surgical procedures. Elective x-ray therapy during the time when it was employed, was used on an elective basis for good risk patients with operable lesions. The poor results (12 per cent five year survival) in this group may be explained by the relatively low dosages that could be achieved by the conventional therapy available at the time. Modern methods would probably give better results, however, it is unlikely that they would be better than those attainable with present surgical techniques or combined techniques.

The results achieved by radical mastectomy are analyzed further in Tables VI, VII, VIII. In the group of patients treated by radical mastectomy the incidence of axillary node involvement is 58 per cent. The minimum and maximum five year survival rates for those with node involvement are 38 per cent

TABLE V
Results of Therapy—Operable Cases

Method of Treatment	% 5 Year Survival	
	Minimum	Maximum
Radical mastectomy	50	55
Simple mastectomy	31	34
Radiotherapy	12	13

TABLE VI
Five Year Survival Following Radical Mastectomy

		Total	Total Determine*	Living	Minimum Percent Survival	Maximum Percent Survival
1932-1936	Without node involvement	35	32	24	69	75
	With node involvement	51	50	16	31	32
	Total	86	82	40	47	49
1937-1941	Without node involvement	43	39	31	72	80
	With node involvement	50	48	16	32	33
	Total	93	87	47	51	54
1942-1946	Without node involvement	38	32	24	63	75
	With node involvement	59	54	24	41	44
	Total	97	86	48	49	51
1947-1951	Without node involvement	46	41	30	65	73
	With node involvement	66	57	30	45	53
	Total	112	98	60	54	61
Total series	Without node involvement	162	144	109	67	76
	With node involvement	226	209	86	38	41
	Total	388	353	195	50	55

* Determinate excludes cases lost to follow-up or dying of intercurrent disease with no evidence of carcinoma.

and 41 per cent. The corresponding rates for those without axillary involvement are 67 per cent and 76 per cent. Table VI shows the influence of the year in which the patient was operated upon. As in other reported series there is a gradual improvement in results in each five year period from 47 per cent minimal survival and 49 per cent maximum survival in 1931, to 54 per cent minimum and 61 per cent maximum survival in the last five year interval 1947 to 1951. The influence of associated radiotherapy is shown in Table VIII. For this analysis cases lost to follow-up, those dying of other disease and postoperative deaths are excluded. This is essential in order that the groups be comparable for obviously a postoperative death cannot be included in the group receiving postoperative therapy. The same consideration applies to a patient lost to follow-up

TABLE VII
Influence of Associated Radiotherapy
Five Year Survival After Radical Mastectomy*

	Preoperative X-Ray			Postoperative X-Ray			No X-Ray		
	Axillary Nodes Not Involved	Axillary Nodes Involved	Total	Axillary Nodes Not Involved	Axillary Nodes Involved	Total	Axillary Nodes Not Involved	Axillary Nodes Involved	Total
Total.....	32	38	70	51	129	180	58	41	99
Living 5 years...	25	11	36	42	58	100	42	17	59
% Survival.....	78%	29%	51%	82%	45%	56%	72%	41%	60%

* "Determinate Cases" only. Postoperative deaths, lost to follow-up and deaths from other causes excluded.

TABLE VIII
Results of Treatment by Radical Mastectomy
Local Recurrence Within Five Years for Different Periods

Year in Which Treated	1931-1936	1937-1941	1942-1946	1947-1951	Total
Total determinate cases.....	77	87	83	97	344
No. with local recurrence.....	21	17	10	8	56
Recurrence rate %.....	27%	20%	12%	8%	16%

shortly after operation. Exclusion of these indeterminate cases improves the overall survival figures but they are presented here solely for comparison between the subgroups. Slightly better results are noted with either preoperative or postoperative x-ray when axillary nodes are not involved. Similar slightly better results are indicated with postoperative x-ray when axillary nodes are involved. Nevertheless there is slightly better overall survival with no x-ray therapy! These discrepancies are attributable in part to differences in the composition of the samples and to the relatively small size of some of the groups. The group receiving postoperative therapy had relatively three times as many patients with node involvement as the other groups. Because of this the improvement in results with such therapy is probably significant.

LOCAL RECURRENCE

There was a high incidence of local recurrence during the early years of the study. The rate progressively decreased in subsequent five year periods. The rates are shown in Table VIII. The decrease in local recurrence is related to the same factors as those responsible for the improvement in survival rates during the same period. Change in the population sample is probably the most important factor and improvement in surgical techniques with more meticulous dissection and wider skin removal is also contributory.

DISCUSSION

This series, like all others in the medical literature, shows substantial improvement in the results of treatment of carcinoma of the breast since modern methods of treatment have been applied. In searching for reasons for the improvement, it is flattering to assume that it is due to improvement in methods of therapy. However, the improvement is noted in reports from centers with drastically opposing views, varying from those advocating a policy of simple mastectomy supplemented by intensive radiotherapy (9) to those treating all patients considered suitable by radical mastectomy and reserving radiotherapy for hopeless and recurrent cases. While noting the improved results of treatment, we have also succeeded in persuading our patients to seek care earlier in the course of their disease and have treated them more promptly. This has undoubtedly improved results but it also makes comparison of present and past results on any other basis invalid since the subject population is decidedly different. Few of the patients we now operate upon with small lesions, would have visited their physician several decades ago, nor would treatment have been instituted at the stage in which many are now seen. As more patients with early lesions seek care, factors of selection become very important in comparing contemporary series. To be valid, any comparison must involve comparable populations. These are difficult to achieve. The best ones for this purpose consist of those in which all patients in a given area go to one institution, but even in such instances, the socio-economic and cultural levels of the communities differ and with this difference there is a difference in the alertness of the population to early signs of illness. Where many hospitals serve one community, differences in treatment policy soon become known throughout the community and influence the types of patients referred for treatment. Series with many private patients differ from those in which most of the patients are indigent. Racial factors are important in influencing the general educational level of the group. In presenting any series of cases, it is therefore extremely important that the nature of the group be defined as precisely as possible.

The importance of these factors is well demonstrated in the paper of Byrd *et al* (10) who compared the survival of patients treated at three institutions in Nashville, Tennessee. There was a striking difference in survival between the group of private patients and the group of municipal hospital patients. This was associated with corresponding differences in average duration of symptoms prior to admission and with the incidence of axillary metastases. The difference in survival rates, however, were also evident in the subgroups with and without node involvement. This would indicate that the incidence of axillary involvement is but one measure of the extent of disease and that other factors are also present in the patients without such metastases in a group with a high incidence of axillary disease.

The variability of this disease has intrigued most men who have written and thought about it. The dramatic instances of prolonged dormancy of metastatic lesions that become active after 10, 15 or more years; the occasional advanced lesions that demonstrate prolonged survival after operation; the occasional

instances of rapid spread and progression of tumors that were apparently treated early and adequately. This capriciousness has led some to a fatalistic attitude and the belief that the course of the disease is determined at its inception and is not appreciably influenced by therapy (11, 12). It cannot be denied that this situation applies for a substantial number of patients when they seek attention.

On the other hand, one has but to watch the untreated disease progress inexorably, in a patient who refuses treatment, extending visibly from month to month causing progressive disfigurement and disability, to be convinced that the removal of such a lesion at an earlier stage does indeed accomplish something. Response to therapy may be seen in the occasional dramatic regression of a previously observed extending lesion following effective radiotherapy.

There is little question that the 15 per cent of patients in most series with detectable distant metastases when first seen are most probably not helped by treatment. Although our ultimate aim is to treat all patients successfully, we cannot use the fate of these patients as a measure of the effectiveness of our therapy. The inclusion of such cases in a series merely dilutes the number of treatable patients decreasing the overall survival figures. Unfortunately, however, our criteria for recognizing these patients are neither infallible nor sufficiently well defined and accepted so as to make the treated group in various institutions comparable. Quite the contrary, these latter variables are so great that the total series in spite of its inadequacies and irrelevancies is probably a better sample than any subgroup. As noted above, however, the total group itself is subject to both obvious and hidden unpredictable factors of selection.

On the other hand, there can similarly be little doubt that the course of some patients has been affected by treatment. Those who had localized lesions when first seen and who after mastectomy never had any evidence of recurrent tumor, would not have been in this state if not treated. In most total series, these amount to at least 15 per cent of all patients seen with carcinoma of the breast. They might be curable even by relatively limited mastectomy.

The remaining 70 per cent of patients bedevil us. There is evidence that radical surgery applied to patients with extensive disease that cannot be extirpated may disseminate the disease and decrease longevity. On this basis, Haagenson (4, 13) has made a substantial contribution by establishing criteria for detecting some of the patients who cannot be expected to do well from conventional surgical treatment. Since most of these patients die from systemic metastases, it is doubtful whether any form of local treatment can help them.

This group of patients also confuses the statistics for variation of criteria of acceptance and of the assiduousness with which these criteria are applied will markedly affect the group treated and therefore the results of treatment. A reluctance to deny a patient possible benefits of aggressive therapy for an otherwise fatal disease even at some risk of aggravation, if the patient's disease later proves to have been unsuitable for this treatment, is quite justified. It will decrease the percentage survival in subsequent statistics even though it may increase the absolute number of survivors.

Perhaps the five year survival rate of an all inclusive sample is too coarse a

measure to detect the influence of therapy. Too many extraneous factors act to round off the result to the monotonous 40 per cent survival for the entire series and 50 per cent for the group treated by radical mastectomy. Of course, selection plays havoc with any statistical analysis and precludes comparison of results from different institutions. But perhaps this type of comparison has no particular validity and we need not strive to attain it. More valid comparisons would be intramural in which patients are selected for treatment by various modalities before the type of treatment is chosen and then the type of treatment is selected in a random manner. This type of comparison and control should yield answers with relatively small numbers of patients that elude retrospective analysis of the treatment of thousands of patients throughout the world.

SUMMARY

The results of treatment of carcinoma of the breast on the ward services of The Mount Sinai Hospital in New York from 1932 through 1951 were reviewed.

Of 543 patients, 29 had previously been treated elsewhere. Fifty-six of the primary cases had obvious systemic metastases on admission. Radical mastectomy was performed on 388 patients, simple mastectomy on 42 and 17 were treated primarily by radiation therapy.

The absolute five year survival rate was 40.8 per cent. The survival rate in determinate cases was 48.5 per cent.

The minimum and maximum relative five year survival rates for all patients treated by radical mastectomy were 50 per cent and 55 per cent respectively.

The minimum and maximum relative five year survival rates for patients treated by simple mastectomy were 31 per cent and 34 per cent respectively.

These rates are of the same order as those reported from most institutions.

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PRIMARY NON-SPECIFIC ULCERATION OF THE SMALL INTESTINE

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The purpose of this paper is to add to the literature another case report of the rare disease entity, primary non-specific ulceration of the small intestine. In addition, the characteristics of the disease will be reviewed briefly. It is hoped that the case history will dramatically emphasize the need to include this entity in the differential diagnosis of gastrointestinal bleeding. In a recent study, Barnett (1) collected 149 cases from the literature. Much of the following information is derived from this excellent review.

ETIOLOGY

Primary non-specific ulceration of the small intestine (PNUSI), as the name implies, is a disease entity of unknown etiology in which there is an ulcer or, less commonly, multiple ulcers of the jejunum or ileum. Trauma, infection, aberrant gastric mucosa, and infarction all have been investigated from the standpoint of etiology, but with negative results. In fact, lack of etiology has been a requirement for including cases in this category. Ulceration of the small intestine following gastroenterostomies and ulcerations due to foreign bodies and neoplasms are excluded from this group by definition. Irradiation can also be ulcerogenic but such lesions also are excluded. Thus the lack of etiology has, paradoxically, been the criteria for classification under this heading.

INCIDENCE

Primary non-specific ulceration of the small intestine can occur at any age. Most patients with the disease are between 30 and 60 years old. Seventy-five per cent of the cases have been in males.

PATHOLOGY

The ulcer has been solitary in 81 per cent of the cases. It has occurred slightly more often in the ileum than in the jejunum. Grossly, the ulcer is a punched out rounded lesion with a smooth base and varies in diameter from three millimeters to about two and a half centimeters. "Microscopically, the ulcer is covered with a thin layer of fibrin and leucocytes. More deeply, the muscularis mucosa is replaced by granulation tissue and is infiltrated with plasma cells and lymphocytes. Varying involvement of the muscle layers with connective tissue

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is also present. Acute ulcerations without fibrosis may occur but chronic ulcers are more usual" (2).

DIAGNOSIS

The diagnosis of primary non-specific ulceration of the small bowel has rarely been made preoperatively. This is because the presenting symptoms are not specific, demonstration of the ulcer radiographically is difficult, perforation, obstruction, or hemorrhage have already occurred by the time the physician is called, and the disease is not considered in the differential diagnosis.

The most frequent clinical finding, before complications, is abdominal pain. Barnett (1), found abdominal pain in 46 of 49 cases. The pain is usually mild, intermittent, midabdominal and unrelated to food or medication. Diarrhea, vomiting, and gross rectal bleeding are less frequent findings. Occult gastrointestinal bleeding with severe anemia can also be the presenting symptoms, as the case history will show.

Most often it is the complications which cause the patient to seek medical assistance. The complications include perforation of the bowel, intestinal obstruction, massive hemorrhage, or some combination of the three. Perforation is by far the commonest of the complications. Barnett (1) found 98 of 130 cases with perforation, 23 with obstruction, one with massive hemorrhage, and a scattering with combinations of the three. In reviewing the records at The Mount Sinai Hospital, many cases of peritonitis were discovered in which a small hole was found in the small intestine. Most of these were closed rather than resected so that no pathologic diagnosis was made. Undoubtedly many were non-specific intestinal ulcers.

The demonstration of the ulcer radiographically is extremely rare. McHardy (3), in a discussion of Morlock's paper, reported two cases investigated for unexplained rectal bleeding in which an intestinal ulcer was demonstrated by x-ray. This was accomplished by intubation with a Miller-Abbott tube through which an iodized oil-barium mixture was injected. At several points aspiration for blood was carried out. Barium meal, in a few instances, has demonstrated a narrowed segment of small bowel at what later proved to be the ulcer site. X-ray examination, of course, is valuable in demonstrating obstruction and free air of perforation when these complications have occurred.

TREATMENT

All literature relating to primary non-specific ulceration of the small intestine states that the treatment is surgical. Yet it is important to remember that the diagnosis has rarely been made preoperatively. No attempt at medical management has been reported. It is interesting to speculate that many patients with mild abdominal complaints may have this disease entity, which, in the course of treatment for "functional disease," spontaneously clears. All of the questions of course would be answered if radiographic demonstration of small intestinal ulcers could be made early in the course of the disease. Insertion of barium through a long gastrointestinal tube at varying levels would certainly be a step

in that direction. When any of the complications such as hemorrhage, obstruction, or perforation occur, surgical therapy is, of course, vitally necessary. Resection with end to end anastomosis is the treatment of choice.

CASE REPORT

On November 17, 1958 a 16 year old white female was referred to The Mount Sinai Hospital as a diagnostic problem. She had a four year history of occult blood in her stool. This was originally discovered at the age of 12 when she was hospitalized for weakness, anorexia, and pallor. Her hemoglobin was found to be 4.5 grams per cent. All gastrointestinal series were negative. The anemia was treated with blood transfusions. She was hospitalized on three more occasions with similar findings, and received a total of 16 pints of blood. Her stools were never grossly bloody or tarry. Occult blood was repeatedly found in the stools.

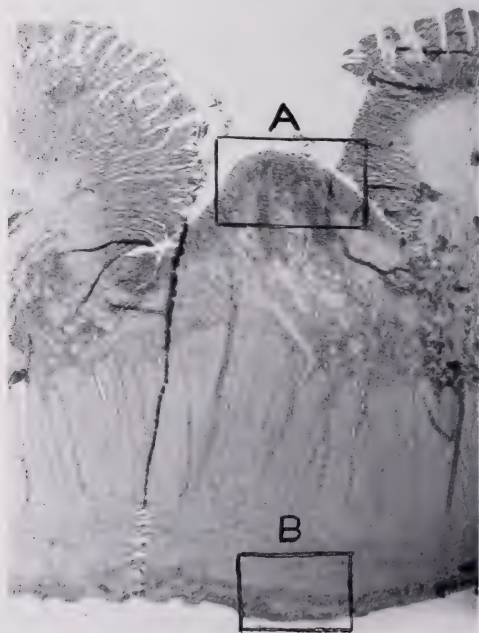


FIG. 1. Longitudinal section through ileum, cutting directly across the linear transverse ulcer. Denudation of mucosa is obvious especially when contrasted with normal mucosa on either side. Deep black vertical lines are artefacts.

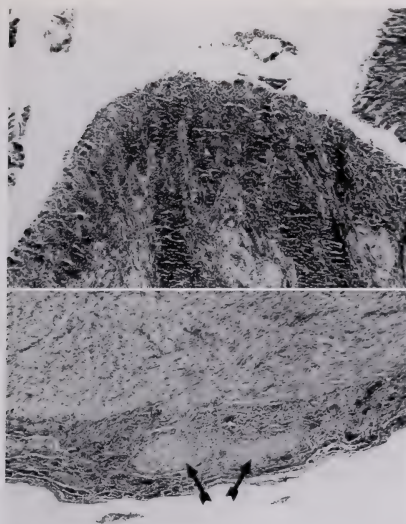


FIG. 1A. High power view of Square A from Figure 1. Note marked infiltration of submucosa with lymphocytes and connective tissue.

FIG. 1B. High power view of Square B from Figure 1. Notice the very marked thickening of the serosa. Two large cords of fibrous scar tissue (See arrows) correspond to transverse white line found grossly at operation.

She complained of intermittent aching abdominal pain in different areas of the abdomen. The pain had no relation to eating or position and did not respond to medication. There was no history of vomiting, diarrhea, constipation, or jaundice. There were no other sites of abdominal bleeding.

Physical examination on admission revealed a well developed, slightly obese, faintly pale, white female in no distress. She showed no signs of acute or chronic illness. There was no abnormal tenderness. There were no abnormal physical findings.

The stool on admission was brown and well formed. The stool guaiac for occult blood was 2 plus. The hemoglobin was 10.9 grams per cent. The white blood count was 7,500 per cu mm with a normal differential. Bone marrow studies revealed only iron depletion. All tests for abnormalities in blood clotting were normal. Gastrointestinal series was negative.

Sigmoidoscopy was performed without abnormal findings. A Cantor tube was passed eleven feet into the small intestine. Samples of intestinal contents were taken at different levels and all were negative for occult blood. At the same time the samplings were tested for radioactive chromate. This had previously been incubated as sodium chromate with 20 cc of the patient's blood and injected intravenously. No chromate was detected in the samplings.

On December 12, 1958 an exploratory laparotomy was performed. About three feet from

the ileocecal valve, a three inch section of dilated ileum was found. There were a few dilated vessels and a two centimeter long, transverse white line found on the serosal surface. the ileum was opened and in the corresponding area of mucosa a four centimeter long, 0.4 centimeter wide, transverse ulceration was found. A one foot section of ileum, which included the area of pathology, was resected and an end to end anastomosis performed. The microscopic findings revealed chronic ulceration (Fig. 1). The ulcer was covered by fibrin mixed with polymorphonuclear leukocytes and lymphocytes (Fig. 1A). The submucosa was infiltrated by connective tissue and a great number of lymphocytes. Scar tissue extended through both muscle layers and serosa. This corresponded with the white line seen grossly on the serosal surface (Fig. 1B).

The postoperative course was uneventful. Repeated stool guaiac tests were negative. The patient was discharged on the seventh postoperative day in excellent condition. Eight months after operation the patient feels well. Her stool continues to be negative for occult blood.

SUMMARY

- A. A case of primary non-specific ulceration of the small intestine is presented.
- B. The characteristics of this rare disease entity are described.
- C. Occult bleeding for four years, necessitating 16 transfusions, was the presenting clinical feature in the case history presented.
- D. Primary non-specific ulceration of the small intestine must be included in any consideration of the many lesions capable of causing gastrointestinal bleeding.

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RELATION OF HEPATIC INJURY TO HEPATIC FIBROSIS*

A PROGRESS REPORT

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In the past year, the following aspects of hepatic fibrosis were studied: (a) mechanism, (b) histochemical features, (c) biochemical changes, (d) immunologic alterations, (e) associated phenomena, and (f) etiologic factors.

The techniques applied included those of light microscopy of routine histologic sections and of ultrathin sections, histochemical analysis, electron microscopy, biochemical analysis, clinical observations and pathologic survey. The guiding theme was a search for the causes of chronicity in liver disease. Many of the studies are not as yet completed, but no attempt is made to separate these in the following presentation.

MECHANISM OF HEPATIC FIBROSIS

Investigations carried out by light microscopy and particularly with the use of silver impregnated sections one micron in thickness were supplemented by electron microscopic studies on the same material (1). The material investigated consisted of livers from autopsies and biopsies including acute hepatitis, fatty metamorphosis, various stages of intrahepatic and extrahepatic cholestasis and cirrhosis, as well as rat livers with diffuse fibrosis produced by ethionine or carbon tetrachloride administration or focal fibrosis produced by intrahepatic carrageenin injection. On the border of the normal liver cell plate, single reticulum fibers are noted in the tissue space surrounded by small amounts of ground substance giving periodic acid-Schiff (PAS) reaction. Electron microscopically, these fibers consist of elementary fibrils with approximately 600 Å periodicity. In routine section they give by overlay the illusion of a basement membrane. A continuous membrane as seen around glandular structures elsewhere is not found. With enlargement of the liver cells as noted in fatty metamorphosis or hydropic swelling and particularly if the liver cell plates broaden as in regeneration or cancer, the reticulum network appears rarefied. In the last two conditions the fibers are thinner as long as the cells are viable. The reticulum framework collapses if liver cells disappear and then reticulum fibers are closely approximated. In thin light microscopic sections their arrangement is irregular and new formation of fibers is indicated by morphologic appearance as well as hydroxyproline determination of livers with extensive collapse (2). Electron microscopically, the excess fibers have normal periodicity. The size of the scars

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depends upon the amount of cells lost. Fibroblasts are noted only in big scars. Around severely damaged liver cells with cytoplasmic clumping as, seen particularly in fatty metamorphosis of the alcoholic (Mallory bodies), in viral hepatitis and in prolonged biliary obstruction, in addition to collapse, fibrogenesis is recognized by closer spacing of reticulum fibers as demonstrated in thin sections by light microscopy as well as by electron microscopy. This new formation differs from duplication of fibers around disappearing plates and is associated with increased PAS positive ground substance and with mobilization of neighboring reticuloendothelial cells which contain large amounts of PAS positive material; fibroblasts, however, are not conspicuous.

Bile ductular cells reveal under the electron microscope luminal microvilli, few mitochondria, and little ergastoplasm. The ductule is surrounded by a continuous basement membrane on the outside of which collagen fibrils adhere which by overlay create the impression of an argyrophilic basement membrane in routine sections. Proliferation of ductules is associated with considerable increase of fibers with heavy collagen reaction ("hyalinization"). Neighboring reticuloendothelial cells are mobilized. Fibroblasts are not conspicuous. Periductular fibrosis contributes in varying degrees to the general fiber accumulation in either human or experimental conditions with diffuse fibrosis. It is particularly important in postnecrotic cirrhosis of man and in ethionine and butter yellow cirrhosis of the rat.

Fibrosis in the portal tracts, in contrast to perihepatocellular and periductular fibrosis, is associated with conspicuous fibroblastic reaction similar to that in connective tissue elsewhere. If experimentally produced by focal injection of carrageenin, it exhibits the same stages as the subcutaneous carrageenin granuloma except that transformation of Kupffer cells to fibroblasts is noted and that a ductular cell proliferation is conspicuous around which fibers are laid down. It responds similarly as the subcutaneous granuloma to various pharmacologic alterations. For instance, in scorbutic guinea pigs, accumulation and calcification of ground substance is accompanied by faulty fiber formation. The hepatic carrageenin granuloma is modified in various experimental hepatic injuries such as biliary obstruction, fatty metamorphosis with or without cirrhosis or experimental postnecrotic cirrhosis induced by ethionine. In man portal fibrosis is found in chronic inflammatory conditions including granulomatosis, in schistosomiasis, in chronic biliary obstruction and particularly around extracellular bile and iron.

All three types of hepatic fibrosis—perihepatocellular, periductular and portal—show the following features: Electron microscopically, the elementary fibrils have the same characteristics and periodicity as in connective tissue under the limits imposed by examination of embedded tissue sections. The new formation of fibers is the result of replication of the same type with aggregation of fibers to bundles and sheets of bundles. No difference can be noted under the electron microscope between reticulum and collagen fibrils. Hepatic fibrogenesis

in any location is associated with accumulation of a ground substance possibly serving as a matrix. It is apparently formed by fibroblasts or reticuloendothelial cells. No evidence was obtained, not even in carrageenin granuloma, that elementary fibrils are formed within these cells, though they seem to form on their surface or near basement membranes. The stimulus for this formation within the hepatic parenchyma is necrosis of liver cells and proliferation of ductular cells. These processes appear to be more important in the common types of cirrhosis than the portal fibroplasia.

HISTOCHEMICAL ANALYSIS

Since the ground substance in which fiber formation seems to take place gives PAS reaction and since fiber formation is associated with accumulation of PAS positive material in fibroblasts and in the liver in reticuloendothelial cells, the distribution of PAS positive non-glycogenic material in the liver was investigated, and the material was histochemically analyzed (3). These studies were carried out on human material and on experimental lesions with various types of graded liver injury including partial ligation of single liver lobes. As a by-product of this investigation, it became apparent that PAS stains of diastase digested paraffin sections offer a simple routine method to visualize the severity of liver cell damage and the distribution of pigments as well as to accentuate other diagnostic features in liver disease. Nonglycogenic PAS positive material is found in the normal liver in centrolobular liver cells around bile canaliculi as interstitial ground substance intermixed with small amounts of acid mucopolysaccharides, and in Kupffer cells both in granular and diffuse forms. Reticulum fibers give the reaction depending on fixation. In liver cell damage, many PAS positive granules appear in liver cells, some of them being biliary pigment or lipofuscin. Similar large granules appear in Kupffer cells. Furthermore, particularly in experimental anoxia and in some human conditions, PAS positive globules occur in the cytoplasm of liver cells. Histochemical analysis indicates at least two different types of nonglycogenic material. One is a carbohydrate-protein compound in the interstitial tissue and in the cytoplasm of reticuloendothelial cells. The second is a lipoprotein in the cytoplasm of damaged liver cells and, in part as a result of phagocytosis, in adjacent Kupffer cells. Evidence exists that the lipoprotein material (lipofuscin) is related to lysosomes found normally in the peribiliary cytoplasm of the liver cells and characterized histochemically by acid phosphatase. In liver injury pigments of various nature probably accumulate in the lysosomes. These studies focused interest on lipofuscin and other pigments whose nature and localization in lysosomes is being examined electron microscopically. In this connection, liver biopsy specimens of eight members of two families with chronic idiopathic jaundice (Dubin-Johnson syndrome) were examined histochemically (4) and different grades from fully developed picture of chronic idiopathic jaundice to almost normal were noted. These observations suggest that the characteristic "black" pigment resembles the pigment noted in

the centrolobular zone around the bile canaliculus in normal livers, but differs from it by an increase in size and number of the individual granules, and extension from the peribiliary cytoplasm throughout the whole cell and from the center of the lobule towards its periphery.

BIOCHEMICAL STUDIES

Characterization of collagen

To demonstrate fiber formation, the concentration of hydroxyproline was used as a point of reference. Its determination in tissues was improved by development of a modification which stabilizes the chromogenic compound characteristic of hydroxyproline after oxidation and condensation with p-dimethylaminobenzaldehyde and the nonspecific interference was eliminated by ratio-spectrophotometry (5). In continuation of previous studies on the rapid fibrogenesis during chronic ethionine intoxication of rats (6), human fibrogenesis was studied under physiologic circumstances as in the infant and under pathologic conditions as in cirrhosis. The hydroxyproline concentration is lower in human infants than in adults, and histologically stainable collagen and silver impregnated reticulum fibers are fewer in babies while in cirrhosis, the total collagen concentration is ten times greater than in infant livers. In both cirrhotic and infant livers the ratio of alkali soluble collagen to total collagen is similar and considerably higher than in control adults. This suggests that fibrogenesis is associated with a relative increase of alkali soluble collagen which is considered to be a precollagen (7).

Enzyme studies

In continuation of investigations previously mentioned (6) in which proline, hydroxyproline and glycine were determined in fractions of liver homogenates during rapid fibrogenesis in the ethionine intoxicated rat, enzymatic alterations during this period were studied and supplemented by similar investigations in other types of fibrosis as well as during recovery. These experiments were performed in groups of rats prepared as follows: (a) 0.5 per cent ethionine diet from one to seven weeks producing a characteristic picture depending on duration of intake; (b) 0.5 per cent ethionine diet for seven weeks followed by basal diet containing 1 per cent methionine for two weeks resulting in mild liver cell injury, slight ductular alterations and fibrosis; (c) 0.5 per cent ethionine diet for seven weeks treated in the last week with cortisone daily (resulting in suppression of fibrosis and ductular cell reaction in some of the animals only); (d) diets containing 0.75 per cent ethionine and 0.6 per cent methionine for ten weeks resulting in mild liver cell damage but virtually no ductular cell proliferation and fibrosis; (e) high fat low protein for 200 days resulting in fatty metamorphosis, beginning ductular cell proliferation and fibrosis; and (f) bile duct ligation 21 days before, resulting in proliferation of ductules and fibrosis. All forms of fibrosis were associated with decreased activity in homogenate of succinic dehydrogenase, glutamic-pyruvic transaminase, glucose-6-phosphatase and proline oxidase (8).

However, the question arises as to what degree fibrosis itself or associated processes such as liver cell loss or necrosis or ductular cell proliferation were important. At present cell counts are carried out according to Daoust for better correlation. According to the evidence obtained so far, the reduction of succinic dehydrogenase and glutamic pyruvic transaminase activity to one-third at the time of the most active ductular cell proliferation and its return to normal during the recovery period is the result of liver cell damage as well as a dilution effect by the excess of ductular cells over the liver cells. The changes of glucose-6-phosphatase activity, a microsomal function, are so far not explained. The proline oxidase activity almost disappears with fibrogenesis of all types and seems to be related to fibrogenesis as well as to liver cell damage. From livers with active fibrogenesis, and endogenous inhibitor of proline oxidase was extracted which affects also the normal liver. It is fat soluble, heat resistant, probably contains long-chain fatty acids and is released on cell breakdown. It may be identical with the U factor of Lehninger and Remmert which uncouples oxidative phosphorylation (9).

Studies on mucopolysaccharides

In view of the demonstration of excess PAS positive material, presumably of complex carbohydrate character, in the tissue spaces during active hepatic fibrogenesis, an attempt is being made to isolate and characterize mucopolysaccharides in normal and fibrotic liver with or without removal of blood by perfusion. So far only small amounts of such material were found in perfused normal liver. It apparently contains uronic acid. Only a very small amount of this material is recovered by alcohol fractionation (10) and none by the cetylpyridinium chloride precipitation (11). In non-perfused liver more mucopolysaccharides are found, apparently of chondroitin sulfate B or heparitin sulfate character, but this is probably of blood origin.

IMMUNOLOGIC ALTERATIONS

Previous studies of the basophilia of the mesenchymal cells in cirrhosis as an indication of the site of gamma globulin formation in experimental animals were extended to human cirrhosis (12). To obtain better information as to the site of gamma globulin formation, Coons fluorescent antibody technique was applied to the same problem. Gamma globulin was demonstrated in some Kupffer cells and in reticuloendothelial cells of the fibrous tracts in various forms of hepatitis and in postnecrotic cirrhosis. In other types of liver diseases and in normal livers, even if the serum gamma globulin level was elevated, few if any gamma globulin containing cells were found (13). In contrast, spleen and lymph nodes revealed increased number of gamma globulin containing cells in all types of hypergammaglobulinemia and no difference was noted between postnecrotic cirrhosis, hepatitis and other types of cirrhosis or non-hepatic hypergammaglobulinemias. The gamma globulin containing cells in the liver were, on cytologic grounds, considered reticuloendothelial cells showing transition into plasma

cells. These cells contain much nucleoprotein and exhibit little or no phagocytosis of liver cell breakdown products. They are assumed to form rather than engulf gamma globulin. It appears thus that the reticuloendothelial cells of the liver in cirrhosis have not only scavenger function and participate in fibroplasia but also form protein possibly of antibody character. Preliminary investigations indicate specific binding of serum gamma globulin in liver diseases to Kupffer cells of livers with the same diseases.

PHENOMENA ASSOCIATED WITH FIBROSIS

Ductular cell reaction

Proliferation of ductules originating from pre-existing ducts or ductules, or, far less frequently, from liver cells occurs in many hepatic injuries, and it is particularly associated with fibrosis in both human disease and experimental conditions. Electron microscopically, ductules in normal and abnormal conditions contain microvilli which indicate secretory or resorptive activity. They are almost always associated with the presence of inflammatory cells, few of which are fibroblasts. To evaluate the extent of the ductular cell proliferation and its relation to fibrosis, chemical analyses were correlated with cytometric observations in the enzyme biochemical studies mentioned above. In the seventh week of the ethionine intoxication, the liver enlarges approximately to twice its normal size, total protein doubles, and a fourfold increase in desoxyribonucleic acid and hydroxyproline occurs, the latter being a measure of collagen. During this period a slight reduction of the total number of liver cells is associated with an approximately 100-fold increase in ductular cells and a fourfold increase in "other" cells which include endothelial cells as well as inflammatory cells not easily separated in cell counting. The dynamic nature of this ductular cell proliferation, as well as of the parallel collagen increase, is indicated by their rapid disappearance upon administration of methionine after the seventh week of ethionine intoxication. A constant ratio between DNA and hydroxyproline in all the experimental conditions listed was found which indicates the close relation between ductular cell proliferation and fibrosis. At the height of the ethionine intoxication, bile flow is greatly increased, possibly related to the ductular cell proliferation.

Liver cell injury

Evidence was obtained by electron microscopy which suggested that some agents, such as carbon tetrachloride or Aramite, produce primary mitochondria injury whereas others, such as dimethylnitrosamine, produce primary microsomal injury. These preliminary observations are at present being coordinated with chemical analysis of cell fractions and with histochemical studies particularly related to demonstration of tissue breakdown products and pigments, and distribution of acid phosphatase.

Portal hypertension

The development of the regenerative nodule in human and experimental conditions has been studied in the presence and absence of fibrogenesis. While

regenerative nodules associated with fibrosis produce portal hypertension those without it do not. This indicates that regenerative nodules alone are not the cause of portal hypertension in cirrhosis and points to the importance of fibrosis. In order to determine the site of the cause of portal hypertension and its relation to histologic alterations, histologic changes in the liver are being correlated with measurements of splenic pulp pressure and wedged hepatic vein pressure in cooperative studies with the Departments of Medicine and Surgery. In schistosomiasis the wedged hepatic vein pressure is normal while the splenic pulp pressure is high (14), indicating presinusoidal portal hypertension produced in the portal tracts. In various cirrhosis, different types of relations were noted.

Cholestasis

In a pathologic survey the site of intrahepatic cholestasis was assumed to be in the bile canalicular membranes of the liver cells (15). Subsequent electron microscopic investigations in both extrahepatic biliary obstruction and intrahepatic cholestasis showed distortion of the normally present microvilli (16). Since the cytoplasm of the liver cells did not show significant alterations, the functional defect was localized into the canalicular membrane of the liver cells. It is assumed that the lesion in extrahepatic biliary obstruction results from increased hydrostatic pressure, while it cannot be decided whether in intrahepatic cholestasis it is primary or is also secondary to increased pressure. From continued investigations on a larger series of material including particularly cases of drug induced intrahepatic cholestasis (17), evidence was obtained that PAS positive material accumulated in the bile canaliculi may contribute to formation of bile casts which produce mechanical obstruction. In both types of cholestasis, connections between bile canaliculi and perisinusoidal tissue spaces may account by regurgitation for at least part of the jaundice. In coordinated histochemical and electron microscopic analyses of bile and dye excretion, the distribution of phosphatases around the bile canaliculi showed characteristic alterations.

ETIOLOGIC FACTORS

In continued study of the etiologic factors of hepatic fibrosis and cirrhosis, histologic observations of the liver in 18 cases of Wilson's disease (18) indicated a postnecrotic cirrhosis varying in stages from completely arrested to very active. Features found particularly frequent were breakdown of fat containing liver cells with accumulation of excessively large Kupffer cells and glycogen degeneration of liver cell nuclei. These features seem to precede the development of cirrhosis and seem to contribute to the irregularly distributed massive necrosis which leads to the collapse characteristic of postnecrotic cirrhosis. A series of cases of schistosomiasis were studied to elucidate the significance and type of the fibrotic lesions in the portal tracts (19). The relation of various drugs to liver injury was surveyed (20). The histologic changes in primary and secondary hemochromatosis were compared and the relation of the iron distribution in parenchymal and mesenchymal cells to liver damage and hemochromatosis was described (21).

SUMMARY

The mechanism of hepatic fibrosis was studied by light and electron microscopy. Fibers aggregate either as result of collapse or of new formation, the latter taking place in the portal tracts in the presence of fibroblasts and around damaged liver cells or around the basement membrane of proliferating ductular cells. In the latter two instances, changes in neighboring reticuloendothelial cells indicate that they assume the function of fibroblasts. The newly-formed elementary collagen fibrils have the same electron microscopic characteristics as pre-existing fibrils and no difference can be noted between reticulum or collagen fibrils. Histochemically, in liver cell damage and active hepatic fibrogenesis, nonglycogenic PAS positive material accumulates in liver and Kupffer cells and in the interstitial space. This is in part a polysaccharide and in part tissue breakdown products of lipoprotein character. Biochemically, new formation of fibers is associated with the appearance of collagen more soluble in alkali and reduction of succinic dehydrogenase, glutamic pyruvic transaminase, glucose-6-phosphatase and proline oxidase activities. The last is possibly related to fibrosis itself whereas the first two may be the result of changes of liver cells and of proliferation of ductules. The latter process can be extremely extensive and highly dynamic. In hepatitis and postnecrotic cirrhosis, modified hepatic reticuloendothelial cells contain and possibly form gamma globulin. This does not take place in other liver diseases or in non-hepatic hypergammaglobulinemias. Intrahepatic and extrahepatic cholestasis are associated with characteristic alterations of the canalicular microvilli of the liver cells.

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THE CHALLENGE TO MEDICAL EDUCATION IN THE NINETEEN SIXTIES*

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A career in medicine has since the beginning of time occupied a unique position in the minds of young men and women and in the hopes and aspirations of parents for their children. Most public opinion polls indicate that more parents select medicine for their children than any other profession. A recent book on the best seller list placed physicians high among those with status in our society. But, cold figures do not indicate that these ideals are put into actual practice.

In Table I are shown for selected years over a thirty year period the number of bachelor degrees granted, the number of applicants to all medical schools in the United States without duplications, and the percentage of the latter in the former. It is clear that with the exception of the war years and postwar years during which there was an unusual situation, medicine has progressively lost its favored position—the percentage of all college graduates applying to medical school has decreased from about eleven per cent to about four per cent.

It may be said that the above is what might well be expected during a time when many other careers have become equally attractive and glamorous, such as engineering, electronics, physics, chemistry and nuclear science. Certainly this is true; as our society becomes more highly developed every group must expect stronger competition. But, let us inspect the figures in Table II on the relation between total applicants to the number of freshmen enrolled. These figures reveal, except for the war years, no improvement and possibly some loss. In the prewar years starting in 1932 the ratio dropped below 2.0 in only two years, while since 1953 it has consistently been below 2.0. The progressive decrease from 1.99 to 1.87 in the last three years may not be statistically significant, but to me it is a cause for concern.

Again it may be said that medicine has about held its own during a time when competition has increased; what more could it expect. Perhaps this is correct, but I am still concerned. In Table III are shown the same ratios for the 25 year period from 1933 to 1958. During a time when medical education has, in response to the needs of the American people, increased enrollment in the freshman class from 6,457 to 8,128, the number of applicants has just held pace in spite of a two and a half fold increase in college graduates.

But, these quantitative features of the situation, about which I have expressed concern, assume insignificance when we review the qualitative features. In Table IV are shown the average college grades of those enrolled in two freshman classes. In September 1950 there were 40 per cent with an A average, 43 per cent with a

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TABLE I
Percentage of College Graduates Applying to Medical School

Year	Bachelor Degrees Granted in Year Ending June	Applicants to Medical School in Year Beginning September	Percentage of Graduates Applying Medical School
1928	111,161	12,420	11.17
1933	137,954	12,128	8.79
1938	164,943	12,131	7.35
1942	185,346	14,043	7.58
1948	272,144	24,242	8.91
1953	304,857	14,678	4.81
1954	292,880	14,534	4.96
1957	340,347	15,917	4.68
1958	365,748	15,791	4.32
1959	—	15,169	—

TABLE II
Relation of Total Applicants to Enrollment in Freshman Classes of Medical Schools

Year September	Applicants	Enrolled	Number Applicants per Enrollment
1932	12,280	6,426	1.91
1937	12,207	5,791	2.11
1942	14,043	6,425	2.19
1948	24,242	6,688	3.62
1953	14,678	7,449	1.97
1956	15,917	8,014	1.99
1957	15,791	8,030	1.92
1958	15,169	8,128	1.87

TABLE III
Comparison of Applicants and Enrollees in 1933 and 1958

	College Graduates	Applicants Medical School	Per Cent of Graduates	Freshman Class	Ratio Applicants
1933	137,954	12,128	8.79	6,457	1.88
1958	365,748	15,791	4.68	8,128	1.87
Per cent 1958 if 1933—100 per cent	265	125		126	

B average, and with a C average, 17 per cent. By 1957 those with A's were only 18 per cent, and those with C's essentially the same at 16 per cent. The increase was in the 66 per cent with B's.

Once again, it might be said, a student with a B average in college is still a good student. Medicine may have lost something, but it still has the better than average college student.

Unfortunately, this is not true if academic success in the freshman year is an index of the mean quality of the students. In Table V are tabulated the number

TABLE IV
Average College Grades of Freshman Medical Students

Average College Grade	Per Cent of All Freshmen 1950-51	Per Cent of All Freshmen 1957-58
A	40	18
B	43	66
C	17	16

TABLE V
Drop-Outs in the Freshman Year

Year	Freshmen Enrolled	Promoted to Second Year	Drop-Outs	
			Number	Per Cent
1954-55	7,576	7,158	418	5.5
1955-56	7,686	7,206	480	6.2
1956-57	8,014	7,470	544	6.8
1957-58	8,030	7,401	629	7.8

TABLE VI
Relation of Drop-Out to Academic Standing

Year	Total Drop-Outs		Good Standing		Poor Standing	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
1954-55	418	5.5	161	2.1	257	3.4
1955-56	480	6.2	156	2.0	324	4.2
1956-57	544	6.8	176	2.2	368	4.6
1957-58	629	7.8	181	2.3	448	5.6

of freshmen enrolled in September, the number in the class after final examinations the following June, and the number of drop-outs for all causes. It is too clear that something serious is happening. During this four year period, when every effort was bent to increasing the input and hence the output of American medical schools, almost half of the increase was lost in the freshman year—211 of 454, a rise from 5.5 to 7.8 per cent.

Some students drop out for personal reasons while in good academic standing. In Table VI are given the number and percentage for each of the four years. There has been little change in the percentage—from 2.1 to 2.0 to 2.2 to 2.3. It follows that the increase in drop outs is almost entirely due to those in poor academic standing. The increase has been progressive; from 3.4 per cent in 1954-55 to 5.6 per cent in 1957-58. This indicates that the medical schools have maintained their standards in face of a decrease in the mean quality of applicants.

Thus, as we enter the seventh decade of the twentieth century, medicine has lost some of its centuries-old favored position to attract a large percentage of the

best minds. And, this has occurred at a time when it is accepted that America and the world desperately need more and better medical care in the coming years. In my opinion medical education can no longer remain complacent and hope for a return of the "good old days". We must busy ourselves with a careful study and analysis of the possible causes for these trends and then we must initiate changes in programs and situations so the trends will be reversed. If we do not, and if the trends continue, medicine will deteriorate and we will fail to provide the physicians which America needs.

I shall attempt such an analysis and then review some of the measures which have been suggested or effected to correct the situation. I hasten to add that little I shall present is original. It has been my privilege, during a ten year period, to serve on the Executive Council and various committees of the Association of American Medical Colleges and to have full access to the comments of my colleagues in medical school administration. Particularly in the last year, I have served on the Committee on Operational Studies of the Association under the leadership of Dr. Lee Powers, Associate Executive Director of the Association, which has been concerned with these very problems. However, I will, when it seems appropriate, express my own opinion.

CAUSES OF CURRENT TRENDS IN APPLICATIONS TO MEDICAL SCHOOLS

All the reasons which have been suggested as causes of the current trends may logically be placed in two categories—those with a short-term effect and those with a long-term effect.

Short Term Effects

There is one specific item in the category of short-term effect. It is the low birth rate of the thirties and the much higher rates of the following years. Let me emphasize that the total figures to which I refer here are of boys and girls who are alive today and are attending high school and grammar school. The only unknown is how many will go to college and how many will not go to college and

TABLE VII
Trends in College-Age Population and Enrollments

Year	Population 18 to 24	College Enrollment	
		Per Cent of College Age	Number
1920	12,989,000	4.6	598,000
1930	15,482,000	7.4	1,101,000
1940	16,607,000	9.0	1,494,000
1950	16,014,000	16.6	2,659,000
1955	15,106,000	18.2	2,755,000
1960	16,237,000	23.3	3,778,000
1965	20,043,000	24.2	4,860,000
1970	24,694,000	26.1	6,443,000
1975	26,360,000	—	—

TABLE VIII
Projections of College Graduates and of Medical School Applicants

Year	College Graduates		Medical Applicants			
	Projected	Actual	At 7.42%	At 4.81%	Actual Number	Per Cent
1956	283,000	311,398	20,999	13,612	14,937	4.80
1957	288,000	340,347	21,370	13,865	15,917	4.68
1958	292,000	365,748	21,666	14,045	15,791	4.32
1959	307,000		22,779	14,767	15,169	
1960	326,000		24,189	15,681		
1961	329,000		24,412	16,835		
1965	454,000		33,687	21,837		

how many will apply to medical school. In Table VII are figures from the office of education on the past and future totals of population of college age and actual or estimated percentages of those who will go to college. The almost doubling in the next ten years is a little staggering when we think of the faculties and buildings which will be needed.

In 1956, while I was president of the Association of American Medical Colleges, certain figures on projections of students were made available to the deans for their guidance in planning the future. In Table VIII are given the figures as projected in 1955 for the next fifteen years. Projections of medical school applications were made on two assumptions, one that 7.42 per cent of college graduates would apply, and second that 4.81 per cent would apply—the low figure up to that time. The projections were as much as 25 per cent below the actual for college graduates, but only about 10 per cent below for the applicants to medical school at the 4.81 per cent level. What I am attempting to say is that there is as yet no evidence that the so-called “flood-tide” of students will have its impact on medical schools.

If the “flood-tide” does not come at least as an ebb tide to the medical school and if there is not some reversal of the trend in the academic level of applicants, there will have to be an “agonizing reappraisal” of many plans. Some schools have projected an increase in the size of classes and many have spoken of new two-year and four-year schools. There is no question we need more physicians, but a supply of able aspirants is not certain at the moment. I am suspending judgment for a year or two to watch the trends, and to do my part in creating favorable trends.

Long Term Effects

Among the long-term effects it is difficult to single out any one as more important than the others; hence, I shall discuss them without regard to relative importance.

Length of Educational Program

One which apparently looms large in the minds of the high school and college student is the length of the educational program. As medical knowledge has in-

creased in volume and complexity, years have been added to the educational program so that today most future physicians who look forward to a career in a specialty spend on an average: four years in college, four years in medical school, one year in internship, four years in advanced training, two years in Federal service.

The mean age on completion is about 33 years, almost half of life expectancy.

The young man or woman compares this with other attractive careers. In engineering he is ready for a job at 22. For advanced physics, chemistry, and related fields he can probably have his doctorate degree and a job at 26. Is there any wonder some ask—is it worth it?—and answer in the negative.

Marital Status of Students

A related fact which may have some influence on these decisions is the changing marital status of medical students. The war years brought about new attitudes toward postponement of marriage until a boy's education was completed. Figures for all medical students in the United States over a period of years are not available, but we do have reliable data for the classes graduating in 1956 and 1959. The per cent married was 55 and 63 respectively and the per cent of those married with two or more children was 12 and 24. The changes in three years are not necessarily a trend, but the change from 30 years ago is very real. When I graduated in 1928 there were not more than eight married students of the one hundred graduates. At that time many hospitals had a regulation that married men would not be accepted for an internship.

For the medical students at State University of New York in Brooklyn in school in 1958-59, further figures are available. Table X shows a significant number, 17, married at registration for the freshman year, and a progressive increase to 49 on registration for the senior year. Table XI gives information on

TABLE IX
Marital Status of Medical Graduates of All American Schools

Graduates in June	Per Cent Married	Per Cent Married with Children	
		2 or more	3 or more
1956	55	12	?
1959	63	24	7

TABLE X
Marital Status of Medical Students in Downstate Medical Center, State University of New York 1958-1959 by Classes at Registration September 1958

	Number Married
Freshmen	17
Sophomores	35
Juniors	38
Seniors	49

TABLE XI

Marital Status of Medical Students in Downstate Medical Center, State University of New York, 1958-59 at Registration September 1958

	Men	Women	Total
Married	123 (23.8)	9 (20.5)	132 (23.5)
With one child	34	2	36
With two children	12	0	12
With three children	0	0	0
With four children	1	0	1
Total with children	47	2	49

the number with children and a breakdown for men and women. The difference between men and women is slight and the number with children is substantial, 38 per cent.

If there are as many of these who face up to a long educational program with a loyal wife, in order to be a physician, I wonder how many more able men and women there are who decide it is not worth the price.

Cost of Education

The length of the program and marital status are related to the cost of living as a student. Fairly accurate figures collected by the Association of American Medical Colleges from the graduates in 1959 are shown in Table XII. The difference in public and private school is almost entirely related to the differences in tuition, and this differential will be increased. I am told that tuition in some private schools next year will be \$1,400 or more. The same graduates supplied information on the major sources of income given in Table XIII.

There are two aspects of these figures I wish to discuss. First, the 21 or 22 per cent of income earned by the student represents a significant expenditure of energy during the school year at the expense of time which could have been spent in study. There is no question in my mind that a significant number of medical students have deficiencies in knowledge because they had to earn money. At the end of every year there are one or two students who have academic failures because of long work hours at night and week-ends.

Parenthetically you may be interested in what the wives of the 123 married men medical students at the Downstate Medical Center in 1958-59 do. The data are given in Table XIV.

Second, the 60 per cent contribution by the family of the single student is really a large amount. Let us look at this in terms of the family income of these same 1959 graduates in Table XV. Perhaps a family can afford 15 to 18 per cent of its total income to keep a son in medical school, but what if there is a second or a third child who wishes to go to college. The percentage soon becomes prohibitive, especially if the one child in medicine has to have some support for up to 13 years after high school.

One of the principles of our democratic society is equal opportunity for all.

TABLE XII
Annual Cost of a Medical Student Graduate of 1959

	Public School	Private School
Single student	\$2093	\$2588
Married student	\$3118	\$3420

Source: Association of American Medical Colleges. Bane Report.

TABLE XIII
Major Sources of Income of Medical Student in 1959

	Per Cent	
	Single	Married
Earnings		
Self	22%	21%
Wife	—	23%
Family	60%	35%

TABLE XIV
Occupations of Wives of Married Medical Students—Downstate Medical Center, State University of New York, 1958-59

	Number	Per Cent
Housewife	37	30.1
Student	16	13.1
Professional (Nurse, teacher, etc.)	49	39.8
Clerical	20	16.2
Other	1	0.8
Total	123	100.0

The motto of State University of New York expresses this well—"Let each become all he is capable of being". Many have been concerned for years that the increasing costs of higher education are pricing it out of the market of a large segment of the people. There is probably no definitive objective answer to the question. I can say that no student who started medical school in any of the three schools with which I have been connected in an administrative capacity in the last fourteen years has failed to finish because he did not have money to remain in school. On the other hand, I know of a goodly number of promising young residents who cut short their training to go into practice because of lack of money when they had not realized all the skills of which they were capable. How many interested, able boys and girls never get to medical school because of insufficient funds is unknown. The only figures I know of which bear on this problem are given in the Bane (1) Report and are shown in Table XVI. The most reliable

TABLE XV
Family Income of 1959 Medical Graduates

Median family income	\$8,375
60 per cent of cost of education	
public school	\$1,258
private school	\$1,553
Per cent of family income	15.0 18.5

TABLE XVI
Per Cent of Families with Different Income

	Per Cent	
	All Families	Medical Graduates
	1951	1959
Under \$5,000	51	20
\$5,000-\$9,999	41	40
\$10,000 and over	8	40

figures for all families in the United States are out of date, 1951, but the distribution then of 51, 41, and 8 per cent is far out of line with the distribution of family income of the medical graduates in 1959 of 20, 40, and 40 per cent respectively. For some reason, financial or other, future physicians are not drawn from the lower economic group in the same proportion this group exists in the nation.

Availability of Scholarship and Loan Funds

Another problem related to costs and income is the availability of scholarship and loan funds. The situation today may be stated simply. The able young man or woman seeking a career in science who elects one of the physical or natural sciences may expect substantial help with a scholarship of nearly subsistence amount for the relatively short period of study for a doctorate. But, the same able young man or woman who elects medicine may expect limited help with scholarships of far below subsistence amounts for the much longer period of study. Figures for the average amount of scholarships given in the Bane Report¹ are reproduced in Table XVII. It should be noted that the figures for graduate students are four years outdated as compared with medical students and hence the differential today is probably even greater. The National Defense Education Act permits loans to medical students, but does not provide any scholarships for medicine, even if the student is willing to sign the disclaimer affidavit.

Inflexibility of Program

Another item under long-term effects I wish to discuss is a broad, but I believe, a very definite one—inflexibility of program. With a few deviations in a few schools every medical student spends four years in lock-step with his fellow students taking the same courses at the same pace regardless of ability or in-

TABLE XVII
Amount of Scholarship Awards

	Amount
Medicine 1958 (mean)	\$512
Graduate 1954 (median)	
Bacteriology	1,565
Biochemistry	1,675
Chemistry	1,520
Physics	1,535
Zoology	1,365

Source—Bane Report.

terests. Perhaps this is necessary in the basic training of the physician, but I am not convinced the matter has been adequately studied. The inviolability of the college curriculum was probably just as firm when Dr. Elliot introduced the elective system at Harvard College. Lock-step education is set to the slowness and intellectual activity of the least able but passable student. The abler student marks time while the tail-end catches up with him. I was shocked two years ago when a small group of able freshmen told me they found the first year of medical school less stimulating intellectually than the last year of college.

Misunderstandings by the Public

The last two items under the broad topic of long-term effects are really not effects but are, I believe, misunderstandings in the minds of the American people concerning the difficulty of gaining admission to medical school and the difficulty of remaining in medical school. How many able boys and girls have never applied because of this misunderstanding is unknown, but I believe there is a significant number so lost to medicine. How many college students have said, "Why apply, I don't have a chance. They take only one out of ten."

This quotation is not a flight of my fancy. Just this fall I received a letter recommending an applicant from an executive of a well-informed and well-researched national news magazine. He said he recognized our problem that we could accept only one out of ten. If he refers only to our school the statement is correct; we have accepted in the last few years 150 out of about 1,250 applicants. But this is not the full and true picture. On an average every applicant for medicine places applications to 3.5 medical schools and for those who apply to the schools in New York City the average is 10 applications per student. The Association of American Medical Colleges maintains a central registry of applicants so all duplications can be eliminated. Some typical figures, similar to those in Table II, are shown in Table XVIII. During the postwar years wide publicity was given to the great difficulty of gaining admission to medical college; and it was difficult, with a high ratio of 1 to 3.62 enrollees to applicants. There were demands for larger classes and more schools. Legislatures and trustees of State schools interdicted acceptance of out-of-state students. Apparently few have

TABLE XVIII
Relation Between Applicants and Enrollees as Freshman
 All Medical Colleges

	Number Applicants	Number Freshman	Number Applicants Per Freshman
1939	11,800	5,794	2.04
1947	18,829	6,487	2.90
1948	24,242	6,688	3.62
1949	24,434	7,042	3.47
1950	22,279	7,177	3.10
1957	15,791	8,030	1.92
1958	15,169	8,128	1.87

TABLE XIX
Multiple Acceptances in American Medical Schools

	For September 1956	
	Number	Per Cent
Total accepted	8,263	100%
Accepted at one school	6,090	74%
Accepted at two schools	1,574	19%
Accepted at three schools	459	6%
Accepted at four schools	113	1%
Accepted at five or more schools	27	—

learned that the situation is back to or below the figures for the thirties when few were concerned. Further, I am not convinced that at present many students who measure up to the standards which have been accepted for medicine are being denied admission. The figures in Table VI bear this out since almost half of the increased enrollment since 1954 has been lost by academic failure in the first year. If we dig deeper, without an increase in quality of applicants, this failure rate will increase. Still further, the competition for the able student is real. At Washington University in 1946 we issued acceptance to about 100 to have 86 register in September. I am told this figure is about 160 today. In Brooklyn for the class of 150 entering in September 1959 we issued acceptance to 252. It follows that multiple acceptances are increasing. In Table XIX are representative figures to show this, and in Table XX are figures for one school, State University of New York, in relation to other schools for one year. Let me repeat, no able qualified student today will, in my opinion, fail to gain admission to some medical school in the United States.

The other misunderstanding is that it is difficult to remain in school. Medical faculties are pictured as slave drivers dedicated to failing as many students as possible. What are the facts? Of the 6,688 students who entered the 77 medical schools in September 1948, eighty-nine per cent were awarded an M.D. degree

TABLE XX

Acceptances by One Medical School (A) in Relation to Others (B, C, etc.)

September 1958

	Accepted Both by School A and Other School	Registered in School A	Registered in Other School
B	43	24	19
C	23	4	19
D	19	14	5
E	12	11	1
F	11	10	1
G	11	8	3
H	9	9	0
I	8	7	1
J	8	8	0

TABLE XXI

Per Cent of Freshman Medical Registrants Who Graduate

Downstate Medical Center, State University of New York

Entered September	Freshman Number	Graduated in Four Years		Total Graduated in up to Six Years	
		Number	Per Cent	Number	Per Cent
1950	148	126	85	134	91
1951	150	127	84	132	88
1952	148	135	91	137	93
1953	150	144	96	145	97
1954	150	138	92	141	94
Total	746	670	89.8	689	92.3

after four years of study. An additional two per cent graduated later. This is a record better than that of any other type of higher education. The figures for five classes at State University in Brooklyn are shown in Table XXI. They are similar to the national figures.

SUGGESTED PROGRAMS TO CORRECT TRENDS IN APPLICATIONS TO MEDICAL SCHOOLS

So much for the problem and the probable reasons for the problem. Now let us turn to what has been done and what might be done to correct the situation.

Active Recruitment

Certainly the first technique which comes to mind is active recruitment in the colleges and in high schools. Traditionally medicine has waited for those interested to come to it. In the 1940's some schools initiated programs in which members of the admissions committees visited colleges and interviewed pre-medical students. This liaison between medical school and college must be im-

proved and expanded. First, the orientation must be changed so there is not only the element of selection for one school, but an element of total recruitment for medicine. The opportunities for a physician as practitioner, teacher, and investigator must be painted in full colors. Groups of high school and college teachers of science might be brought to the medical school for visits or for summer work-shops which would acquaint them with the activities of a medical school and at the same time lead to improvement of the teaching of science. Techniques which are even closer to Madison Avenue are at hand. The Association of American Medical Colleges and American Medical Association have prepared a film on the "Career of a Physician" to be shown to young people.

Shortening of the Total Period of Study

A second category of possible correction is shortening of the total period of study. It is customary in educational circles to ascribe any present padding of the program to someone else. Thus the medical educator blames the colleges, and the college professor believes the wastage is in the high school. The high school teacher lays the blame on grammar school, and at this point there is a sign, "The buck stops here." Be that as it may, medicine should tidy up its own house without regard for others.

The real question is—can the program be shortened without loss of quality. Many believe it can. Many schools accept students after three years of college. Our faculty has instructed the admissions committee to increase this percentage if at all possible. Johns Hopkins has this last Fall started a program of admitting selected students after two years of college into a transitional third year of college and medicine. A number of schools are studying the possibilities of a program of two or three years of combined college and medical school instead of the present sharp break.

Then there is the internship, for which we have disagreement even in how to define it. The internship was developed to give the young graduate an educational experience in practice at a time when the junior and senior years were largely didactic and formal education. It was needed and was further education. Today the last two years of medicine are clerkships with extensive experience in supervised practice, yet we still have the internship. If the graduate twenty years ago needed an internship before going on to a residency, the graduate today is more than ready for a residency. And, in addition to all this the internship in many hospitals has lost its essential educational basis, and is much more than just practice. Is it any wonder that graduates are more and more electing straight internships, which are really first year residencies, except in name, and are shunning certain institutions?

Longer Academic Year (Acceleration)

A third category of possible correction is lengthening of the school year, which in some situations is acceleration. How can we defend a plan which was designed for another period and for those of a different age. In early rural America children were needed on the farm in the summer so the school term was nine months. It

TABLE XXII
Length of School Year

Annual Session of Weeks	Number Sessions	Total Weeks of School
32	4	128
36	3.6	128
40	3.2	128
44	2.9	128
48	2.7	128

was also believed a long summer vacation was needed for rest, study, as at Oxford, and for maturation. I can not accept any of these reasons in 1960 for highly selected adults in their early twenties. Their colleagues who did not go to medical schools have jobs in business and industry and probably get all of two weeks vacation a year. As shown in Table XXII, if four sessions of 32 weeks each are standard for 128 weeks of school, this total time can be attained in 3.6 sessions of 36 weeks, 3.2 sessions of 40 weeks, 2.9 sessions of 44 weeks, and 2.7 sessions of 48 weeks. It is clear that four school years of time can be put into three and still have about 10 weeks of vacation a year. I am not at all convinced a plan of this type is impractical for medicine and would in any way lower quality.

One objection, among many which have been offered, relates to the loss of earnings in the summer by students. Let us examine this in terms of cold economics and not emotions. Assume optimistically that the student earns \$800 clear each summer for three summers, a total of \$2,400. On the accelerated schedule he would graduate one year earlier and thus have at some stage in his life an additional year of earnings as a physician. Assume this comes ten years after he starts and that he borrows the money at six per cent to accelerate. He would pay interest on \$800 for 10 years, another \$800 for 9 years, and another \$800 for 8 years. It has cost him \$3,696 for the loan and interest to replace earnings. Certainly this is a fraction of what he can earn in a year as a physician, and he is financially ahead by accelerating.

Programs with Greater Opportunities for Abler Students

A fourth category of possible correction is the development of educational programs which give greater opportunity for the abler students. Here we are concerned with the problem of what I earlier called lock-step education. There are two possibilities—qualitative and quantitative.

On the qualitative side we have so-called "honors programs" such as have been developed at New York University. The abler student is given additional educational opportunities in the form of seminars, lectures, and in research. In other schools such as our own there is only the opportunity to do research during the year or in the summer.

On the quantitative side I would like to suggest a combination of acceleration and greater opportunity, both in relation to large classes. The ever increasing demand for more physicians and larger classes is a challenge to medical schools.

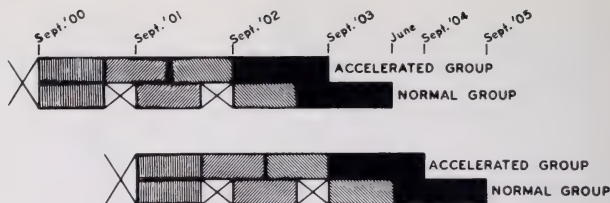


FIG. 1.

A large part of medical education requires small group teaching to preserve quality. How can we attain the former and preserve the latter? The University of Tennessee has for many years admitted 50 students a quarter so they in fact have annual classes of 200, but classes for instruction of 50. The drawback is that a much larger faculty is needed and legislatures and trustees are reluctant to supply the needed funds.

There is another possibility as illustrated in Figure 1. A class of, let us assume, 200 is admitted in September of year '01. They all take the first year course together with sufficient faculty to provide for small group instruction. Toward the end of the first year, there is bilateral selection so the class is divided into two about equal halves; one half is the abler group. They will go on an accelerated schedule and graduate six to nine months earlier than the second half which will proceed at the old pace. Further the faculty will be adequate for two separate classes and the abler group will have different courses with more advanced elements.

You may say this will send into the world two kinds of physicians—the abler and the less able. Perhaps it will, but is that not true of all education? This only recognizes what exists, and promotes it. It keeps the lower level of ability where it now is, but raises the highest level higher.

There is still another point about ability, particularly in relation to economic resources. Medical education has always been conducted on the all or none principle—full-time or not at all. In most other areas of education the part-time student is welcomed or even encouraged. I don't know the answer, but I wonder why it is not possible for a student to take gross and microscopic anatomy the first year, biochemistry and physiology the second year, and similarly divide the subjects of the sophomore year. In the last two years with the block clerkship schedule anything is possible. Such a program as this might make it possible for more of the really able boys and girls with limited resources to study medicine. It might make administrative problems in the dean's office, but we do not run the medical schools to make the life of the dean easy. If we did, they would have closed long ago.

Program Flexibility in Relation to Interests

A fifth category of possible correction is greater flexibility in relation to interests. Here again I refer to lock-step education. With the exception of a few

schools, everyone takes the same amount of every subject (156 hours of this and 419 hours of that). Further, these required hours fill the hours of the week.

Recently there has been a trend to create more so-called "free time" in the curriculum. In Brooklyn three years ago the faculty reduced the required work so that three half days a week plus Saturday afternoon were free; in other words, 4 of 12 half days, or 33 per cent, were free. At the same time elective courses were organized so each student could further explore the subject which most interests him. Further, a full quarter of nine weeks in the senior year was made elective.

A further aspect of this problem is the interrelation of the natural and social sciences and the humanities. Every medical school pays lip service to a general liberal education at the college level, but the moment we get the student, we arrange a schedule of science such as to make it impossible for him to continue even a limited interest in any other subject. Medicine is no longer just a biological science. It is equally a social science. The physician should be an educated man with an appreciation of society. Some of the free time should be available for those who desire to continue other studies. In isolated medical colleges such as ours, this will require a department of general studies, such as have been established by isolated colleges of engineering with great profit.

Physicians do many different things, but there are two large groups, those who have a career in practice and those who have an academic and research career. Some of the faculty at Pittsburgh have suggested we design two programs which diverge in the later years. I don't believe the plan is sound, but the idea of program in relation to interest is there. I believe the future physician, be he practitioner or researcher, should have the same minimal content in his medical education. This development should come in the postgraduate years.

The final aspect of program in relation to interest to review here is that of combined medical and graduate study. If medical education is to be expanded in the next decade, trained able faculty in large numbers will be needed. Today, there is an increasing number of students interested in a combined Ph.D.-M.D. program. When, in 1928 after graduation in medicine, I registered in the graduate school of Western Reserve University as a candidate for a Ph.D., I was something of a freak; perhaps I still am. But, there is now a demand and a need. We must meet it. The University of Indiana has just initiated such a program. A number, not exceeding twenty students of the freshman class by bilateral selection, will remain on the Bloomington campus to do the first two years of medicine and a doctorate program ending in a Ph.D. They can then go to Indianapolis for the last two years of medical study. At Rochester for many years students have been encouraged to drop out after the second year for a year of research and/or graduate study. Other schools are now doing this and the U.S.P.H.S. has made available fellowships for this purpose.

Programs with Greater Intellectual Stimulation

The sixth category of programs with greater intellectual stimulation is one more related to the quality of teachers and teaching, but there are some aspects which may be treated at the school level.

A point which has interested me for some years is the essential sameness of the junior and senior year. Many seniors say frankly they feel let down. Education to be stimulating must be progressive, each step must be a little higher and more advanced than the last. In Brooklyn we are studying a plan in which the medical student would become a student physician during one half of the senior year, with all the implications of this change in name. The student-physician would have his own office in the new University Hospital and see all his patients there. He would follow each patient into and out of the hospital. Disease is no longer an isolated event, but a part of the life of a living human being. The patients are his patients. The faculty become consultants to whom he comes for supervision and advice.

Earlier Acceptance of Students

The earlier acceptance of students has been urged by many. I believe we should experiment with it. There are many premedical students today who are sincerely convinced there is only one way to gain admission—take every science course offered whether it is of any interest to that student or not. I do not discourage the student who is interested in science, but I believe the world has lost something if the premedical student deeply interested in sociology, or history, or Greek does not pursue this interest.

Would it be catastrophic if we did something like this: At the end of the freshman year of college we selected a group of the really able premedical students and said to them, "You will be admitted to medical school in due course if you preserve about the same level of academic success you have demonstrated this year. Now go ahead and take the bare minimum of required subjects with whatever else most interests you. Stop competing for a hundredth of a grade point over your fellows. Get yourself a good education. We will follow your career and admit you to medical school when we think you are ready, after three years, after four years, or perhaps earlier." I believe we would produce better educated men and women for medicine under this plan.

Availability of Scholarship and Loan Funds

There is little I need say about greater availability of scholarships and loan funds. The need is clear and great. The guaranteed loan program of the State of New York has been of some help. The loans under the National Defense Education Act have been small but useful. It is encouraging that the House of Delegates of the American Medical Association just last month in Dallas instructed the administration to study the problem. I have always believed that the greatest responsibility here was on the medical profession in general, and the alumni in particular. The last generation must help the next generation, not only as a total nation but in each group within the nation.

Adequate Housing

Again, adequate housing at reasonable rates, particularly for married students needs little elaboration. In large urban centers such as New York this is especially

true. We have a few students who spend four hours a day commuting to and from school. This is bound to have an influence on their academic standing. More important than convenience and expense, is the need to bring students together outside the classroom, not in a paternalistic sense, but in the creation of an environment of serious scholarly achievement. For decades, American education has concentrated on the time period from nine to five. We must give some attention to the time period five to nine. Oxford and Cambridge learned this centuries ago. Colleges such as Harvard and Yale profited from this lesson. We need educational residence halls, not dormitories.

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Clinico-Pathological Conference

HYPERTROPHIC GASTRITIS, HYPOPROTEINEMIA AND ANEMIA

Edited by

FENTON SCHAFFNER, M.D.

A 66 year old retired white male (waiter) was admitted to The Mount Sinai Hospital for the fourth time. He complained of dark urine, light stools, loss of appetite for two weeks, and jaundice for one day. Six years earlier he noted abdominal cramps, weakness, anorexia and a 10 pound weight loss over a period of two months. At the Consultation Service of this hospital, he was found to have peripheral edema, anemia, leukocytosis, hypoalbuminemia, cholelithiasis and an abnormal gastric roentgenogram. Because of the x-ray finding, he was admitted to another hospital where a total gastrectomy, splenectomy and distal pancreatectomy were performed. The pathological diagnoses were giant hypertrophic rugae of the stomach and myeloid metaplasia of the spleen. The patient experienced about a month a temporary improvement following surgery and then became weak. He lost 40 pounds in the year after surgery and developed generalized anasarca. Each day he had five to six light-colored, bulky, foul-smelling stools associated with occasional painless abdominal rumbling.

Because of the above symptoms he was first admitted to The Mount Sinai Hospital one year after surgery. At that time he appeared emaciated and weak. The vital signs were normal. He had generalized anasarca and ascites. Dulness was present in the left lung base. A grade 2 systolic murmur was heard over the entire precordium and serous fluid was seen draining from a scar in the right upper flank.

The hemoglobin was 6.5 Gm% and the WBC was 35,000 per cu mm with a normal differential count. The bone marrow was hypercellular and normoblastic and the anemia was macrocytic. The stools were guaiac negative and contained no excess neutral fat but many fatty acid crystals were seen. The glucose tolerance curve was normal. The serum vitamin A rise from 13 mcg% to 26 mcg% in six hours during a vitamin A tolerance test. The serum carotene level was 26 mcg%. The total serum proteins were 4.9 Gms% with an A/G ratio of 2.5:2.4. Bromsulphalein retention was 10% in 45 minutes. The serum alkaline phosphatase was 20.9 KA units, BUN was 24 mg%, serum cholesterol 71 mg%, serum phospholipids 120 mg%, serum amylase 45 units and the prothrombin time was 15 seconds with a control of 12 seconds. A secretin test showed normal volume and amylase but a low bicarbonate consistent with pancreatic insufficiency. Icteric index studies of the duodenal fluid suggested a nonfunctioning gallbladder. X-ray studies showed a left pleural effusion and a well-functioning esophagojejunostomy with no evidence of obstruction or intrinsic inflammatory disease. Excessive amounts of secretion were present in the bowel. Transit time was delayed and late segmentation of the barium column occurred in the ileum and also in the jejunum. The sinus tract in the abdominal wall did not communicate with the gastrointestinal tract.

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

The patient was treated with blood, albumin and steroids over a period of four months in the hospital. He continued to lose weight but he felt better and the number of bowel movements was reduced.

The patient's condition remained stable for two years without weight gain and without diarrhea. He was unable to work because of weakness and swollen ankles. He then began to lose his appetite and became progressively weaker. He was readmitted to the hospital with abdominal discomfort and bone pain after three months of increasing difficulty. He was found to be cachectic with a blood pressure of 90/60. A few coarse rales were present in the left base. The heart was enlarged and a soft systolic murmur was heard over the precordium. No abdominal organs or masses were felt. Mild edema and stasis dermatitis were present over the lower extremities.

The hemoglobin was 5.0 Gm% and the WBC was 37,200 per cu mm with 78% segmented cells, 4% band forms, 12% lymphocytes, 2% eosinophiles, 3% basophiles and adequate platelets. The marrow was hypocellular and some megaloblasts were seen. The urine contained urobilinogen in dilutions of 1:40. Serum albumin was 3.3 Gm% and globulin 2.9 Gm%, BUN 22 mg% and cholesterol 106 mg%. The prothrombin time was 15 seconds with a control time of 12 seconds. Cephalin flocculation was 3 plus. A glucose tolerance test was normal. Serum bilirubin, alkaline phosphatase, calcium and phosphorus concentrations were normal. Stool examinations showed intermittently positive guaiac reactions, neutral fat and fatty acid crystals. Absorption of tagged cyanocobalamine which was low improved when intrinsic factor was given. A d-xylose test was normal. An x-ray examination of the chest revealed the left leaf of the diaphragm to be elevated and the left costophrenic sinus to be obliterated. Extensive skeletal demineralization was seen with wedging of several lower dorsal vertebral bodies. The small intestine and colon were reported to be normal.

The patient was given blood transfusions, serum albumin, parenteral vitamin B complex and vitamin B₁₂, liver extract and folic acid. Oral iron and steroids were also given during part of the hospital stay. An 8.2% reticulocyte response occurred during the second hospital week but this gradually decreased to less than 1.0%, and the patient's hemoglobin ranged from 5 to 9 Gm% despite many transfusions during his four months of hospitalization. He improved slightly and was discharged to the Outpatient Clinic.

For six months he did fairly well and then was admitted for the third time because of increasing weakness and diarrhea. Physical findings were as before but in addition the skin was noted to be darkly pigmented and the liver was felt one fingerbreadth below the right costal margin.

The hemoglobin was 6.7 Gm% and the WBC was 27,150 per cu mm. Hypochromia and macrocytosis were present. The blood chemistry findings were essentially unchanged with the exception of the serum alkaline phosphatase which had risen to 18.8 KA units and serum calcium which had dropped to 6.7 mg%. Fecal fat was 16.1 gm per day. Thyroidal I¹³¹ uptake was 43% in 24 hours. The bone marrow was hypocellular with reduced red cell elements but no megaloblasts. Some myelofibrosis and megakaryocytic myelosis was reported. Extensive demineralization of bone again was seen with wedging of several

vertebrae. No new findings were noted on any of the x-ray studies. ECG showed a first degree AV block and nonspecific T wave changes in leads 3, aVL and aVF.

The patient was given blood, vitamin D and calcium. Intravenous fat emulsion also was given for a short time. After 2½ months the patient had gained 10 pounds, his hemoglobin was just above 10 Gm % and he was sent to a convalescent home.

Following his discharge from the hospital, the patient returned once or twice a month to the Hematology Clinic for blood transfusions. After his last transfusion he noted increasing anorexia and edema, dark urine, light stools, malaise and pruritus. He lost his taste for cigarettes but had no pain or gastrointestinal distress. After ten days he was deeply jaundiced and was admitted to the hospital for the fourth and final time.

On examination he was afebrile, extremely emaciated, lethargic and deeply icteric with a green-gray hue. Many excoriations of the skin were present. Feto hepaticus was noted. Bilateral lenticular opacities, kyphoscoliosis, left basilar rhonchi, and a harsh systolic murmur over the entire precordium were found. The liver was tender and felt two fingerbreadths below the right costal margin. Severe pitting edema and stasis dermatitis were present on the legs. The nailbeds were cyanotic but not clubbed. The prostate was twice its normal size and smooth.

The hemoglobin was 6.0 Gm % and the WBC was 49,200 per cu mm. Bile and urobilinogen were present in the urine. The serum bilirubin was 22.8 mg %. serum alkaline phosphatase 22 KA units, serum glutamic oxaloacetic transaminase 218 units, cephalin flocculation 2 plus, thymol turbidity 10.5 units, blood ammonia 1.1 mcg/ml, serum cholesterol 151 mg % with 81 mg % esters. Serum albumin was 2.6 Gm % and globulin 4.3 Gm %. BUN was 34 mg %. Blood sugar, CO₂, chlorides, sodium, potassium, calcium and phosphorus were normal. Prothrombin time was 28 seconds with a control time of 12 seconds. It decreased after intravenous vitamin K to 25 seconds. The serum mucoproteins which had been high (79 mg %) on previous admissions were now slightly low (47 mg %). No new x-ray findings or electrocardiographic changes were reported. Two attempts at sternal marrow aspiration yielded only peripheral blood.

The patient was given blood transfusions and parenteral calcium and vitamin K. He remained afebrile and his jaundice began to abate, the serum bilirubin having dropped to 6.6 mg % after three weeks. At the end of a month in the hospital, he developed a fever of 100°F., diarrhea, left lower quadrant pain and tenderness, absent bowel sounds and hypotension. He was found dead the following morning, 5½ years after the onset of his symptoms and five years after surgery.

*Dr. David Adlersberg:** Dr. Wolf, would you be kind enough to discuss the x-ray findings?

* Late Associate Attending Physician (for Metabolic Diseases), The Mount Sinai Hospital, New York.

Dr. Bernard Wolf:† Before showing the x-rays, I would like to read the report of the early examination done by Dr. S. A. Brahms, because those films are not available. "Barium meal examination showed no intrinsic abnormality in the esophagus. Practically the entire stomach with the exception of a short prepyloric segment was the site of huge increase in the size of the folds. These were seen in the fundus and the distance between the diaphragm and what appeared to be the fundus of the stomach was increased. The wall of the stomach was soft and pliant throughout and peristalsis was actually observed to traverse the body of the stomach. On the lesser curvature aspect of the stomach (in the vertical portion), there was an apparent filling defect which may have represented a number of closely apposed thickened folds or actual confluence of folds. A discrete ulcer was not identified. The duodenal bulb and duodenal loop were normal in appearance. Although the appearance would probably have been due to simple hypertrophy of the gastric folds, the most likely diagnosis was that of lymphosarcoma."

We have a few films taken on his earlier admission. A chest x-ray taken in 1955 showed a pleural effusion on the left side of mild degree and also some fluid on the right side. The hilus was not particularly large in the absence of cardiac enlargement. A film taken on the second admission demonstrated marked kyphosis of the spine with collapse of the bodies of D7 and D8. There was no evidence of any discrete destructive lesions.

The small bowel series done on the first admission to the hospital showed the total gastrectomy. The proximal loops of small bowel were slightly dilated but not remarkably so. The transit time of barium through loops of small bowel was delayed. Also, some barium remained in the jejunum (Fig. 1). Abnormal secretion and segmentation of mild degree was consistent with the so-called malabsorption syndrome. In most cases where we see dilatation, we think of pancreatic insufficiency on the basis of carcinoma of the pancreas.

Dr. Adlersberg: There are several very interesting features in this case that deserve discussion.

He was operated upon with the preoperative diagnosis of lymphosarcoma which was then revised to hypertrophic giant rugae gastritis. There is great interest now in this and similar conditions because they represent the possible source of protracted and severe protein loss. Physicians have been interested for many years in a condition which had been called "idiopathic hypoproteinemia." This term has been changed to "hypercatabolic proteinemia" and this should indicate that in the presence of pronounced hypoproteinemia, an increased catabolism with increased destruction of protein is noted (1). Very recently a group of workers at Bethesda (2) and also in Copenhagen (3) proved convincingly that loss of protein occurs into the stomach or into the small or large bowel, and hence the latest term "exudative gastroenteropathy". Gordon (1) in Bethesda used a special technique in which polyvinyl pyrrolidone (PVP) a giant molecule labeled with I^{131} , was employed. This substance had been used during the war

† Radiologist, The Mount Sinai Hospital, New York.



FIG. 1. Roentgenogram of upper small intestine showing mild segmentation and barium remaining in the jejunum.

as a blood substitute. It is unaffected by proteolytic enzymes. Labeled PVP is injected and the excretion of the substance can be studied in the feces. Gordon had patients with hypertrophic rugae who had ninefold excretion of this labeled substance into the stomach (2). As a matter of fact, in two cases in Copenhagen, the stomach was removed because of this diagnosis to prevent the steady loss of protein (3). Unfortunately, one of them died during the postoperative course. However, such a condition may be also encountered in the presence of gastric carcinoma and gastric sarcoma. Leakage may take place in the small bowel, in some rather atypical cases of sprue or malabsorption. It is quite possible that the hypoproteinemia our patient presented throughout his observation period was the result of exudative gastropathy or later enteropathy.

Another point of interest is the malabsorption syndrome. Whether prior to total gastrectomy he also had evidence of malabsorption is not known. After operation he had steatorrhea and the clinical picture of sprue with x-ray changes of small bowel compatible with such a diagnosis, and the question arises whether he had primary or secondary sprue. Primary sprue, according to our present concept, is a heritable metabolic defect which results in abnormal enzymatic mechanisms in the mucosa in the bowel and prevents absorption, whereas secondary sprue is caused by a variety of pathologic conditions involving grossly the small bowel: lymphosarcoma, amyloidosis, jejunoileitis or Whipple's disease.

There are one or two findings that must be interpreted as against the diagnosis of primary sprue. In other words, he could have been a patient with the inborn defect of absorption who, after total gastrectomy, developed manifest symptoms of this disorder, but I would not believe this reasoning is correct. First of all, during his first hospitalization, after the operation a jejunal biopsy was done.

It showed perfectly normal villi in the mucosa of the jejunum. In a case of malabsorption with secondary osteomalacia, bone deformity, high alkaline phosphatase and the prolonged course of diarrhea, the architecture of the jejunal mucosa would be abnormal. The patient did not show that.

Also against primary sprue was the result of the Schilling test. There was low absorption of labeled vitamin B₁₂ which improved after the intake of intrinsic factor. This finding is seen in patients with pernicious anemia and in patients who have no stomach. The typical primary malabsorption syndrome shows no improvement with intrinsic factor because it is not the lack of this factor that causes malabsorption. We would rather believe then that this was an instance of secondary malabsorption. We see occasionally severe secondary malabsorption after total or even partial gastrectomy. Our patient might have had lymphoma, lymphosarcoma, or amyloidosis of the gut undiagnosed during life. I am prepared for a pathologic diagnosis from Dr. Popper explaining the secondary malabsorption syndrome which I consider more likely than the primary.

He died with jaundice. He received numerous blood transfusions, and we believe he had hepatitis, perhaps with some hemosiderosis in addition, because of the large quantities of blood given. A less likely possibility is a carcinoma with metastases in the liver.

Finally, he died with absent bowel sounds, although this could be an agonal change in a very sick patient. I would like to mention the possibility of a rare but very grave complication in sprue, namely, volvulus of the large bowel. We have seen two of them die suddenly with volvulus of the sigmoid. I did not consider this condition seriously in our patient.

I think that this man had essentially a giant rugae gastritis with exudative gastropathy. After total gastrectomy he had malabsorption syndrome, probably of the secondary variety and exudative enteropathy. He had jaundice, probably viral hepatitis, with hemosiderosis, and I am prepared for some surprises.

Dr. Hans Popper:‡ Do you think that a second disease, of a hematologic nature, existed?

Dr. Adlersberg: We thought all the time that perhaps he had an associated hematological disorder because of the large spleen, the myeloid metaplasia and also the steady presence of leukocytosis of 20,000 to 50,000 white cells per cu mm.

Dr. Popper: We were fortunate enough to receive from Memorial Hospital a picture of the resected specimen. The patient came to operation there with the diagnosis of lymphosarcoma and was found on examination to have a very large spleen. The stomach revealed no tumor but had giant rugae. The original slide of the stomach showed the normal mucosa with large polypous excrescences (Fig. 2). These indicated that there was no involvement of the muscular layer or submucosa. It was a fairly normal stomach with a tremendous overgrowth of the surface layers. The surface layer was thrown out into folds with very close

‡ Pathologist-in-Chief, The Mount Sinai Hospital, New York.



FIG. 2. Appearance of the stomach removed six years earlier showing polypoid excrescences of mucosa. The spleen and pancreas are in the upper right hand corner.

contact between capillaries and the epithelium, but with normal surface epithelium gland cells which probably did not secrete anything except apparently serum proteins, particularly albumin (Fig. 3). The question is always raised whether there is a leakage through normal epithelium or pre-existing ulcers. We found in the specimen given us a few areas of hemorrhage and there was indeed the possibility of loss of protein through hemorrhage but we assumed the hemorrhage was less important than seepage through a normal epithelium. The question is always raised whether this represented gastritis, the result of an inflammatory epithelial hyperplasia, or whether it was a tumorous benign overgrowth. The histological picture in this instance, like in many others (4-6), was quite characteristic and despite re-occurring evidence that this may have led to inflammation, we were quite sure in this case we were dealing with an actual overgrowth in the sense of a villous adenoma and not a response to an inflammation (Fig. 4).

When the stomach was removed the spleen was taken out and found to have a normal architecture. Infarcts were absent and follicles were perfectly preserved but very much in the background compared to the tremendously extended and overgrown and varied cellular pulp. There were a large number of blast cells not easily recognized as red cells or white cells. There were a large number of immature cells which quite readily fit into the picture of myeloid metaplasia with overgrowth of the white and red cells as well as a large number of usually compressed megakaryocytes. Reticulum cells were proliferated, some of them resembling fibroblasts and also many fibroblastic elements were seen. As a result efforts, fiber formation was apparent. Iron stains failed to show any increase in iron at this time.

The lymph nodes removed were not involved in the process because the architecture in several sections was perfectly normal. In the medulla a few large blastic cells were found possibly belonging to the picture of myeloid metaplasia but surely not diagnostic. An entirely normal pancreas was removed.

When the stomach had been removed, the source of the presumed loss of the protein was gone, but as Dr. Adlersberg has told you, no change occurred in the hypoalbuminemia which originally brought the patient to the hospital in a state of emaciation. It appears to me that if there was an exudative gastropathy, the removal of the stomach should correct the protein loss. There is one case on record in the very small series of cases in which escape of large molecules had

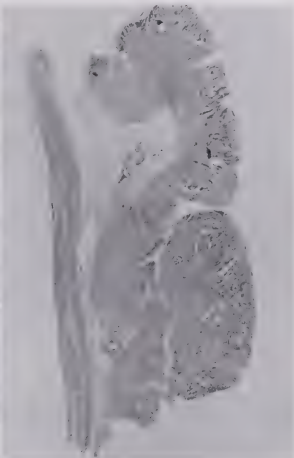
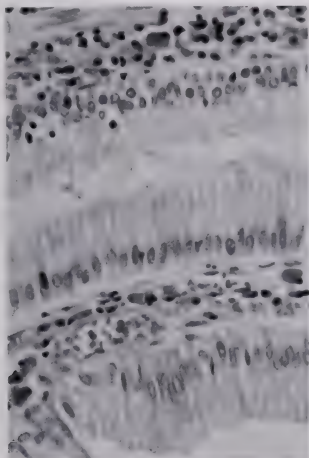


FIG. 3. Section of stomach showing close proximity of capillaries to surface epithelium (H & E $\times 400$).

FIG. 4. Hypertrophic gastritis involving the surface epithelium as in a villous adenoma but showing no inflammation (H & E $\times 4$).

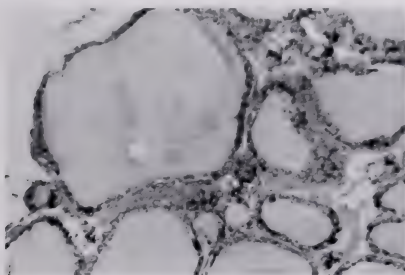


FIG. 5. Thyroid gland showing iron deposition in the cells of the follicles (iron stain $\times 120$).

been demonstrated in which the loss of protein subsided after the successful removal of the stomach (2).

At the autopsy, our first interest was in clearing up the question of the hematologic disorder. On inspection of a specimen of bone, we saw osteoporosis with osteoclasia in quite a few areas as well as increased cellularity of the marrow. It was not easy to identify the different elements. Many reticulum cells and fibroblastic elements crowded the marrow. We got the impression of strands of what may have been fibers, especially around the cells. We saw a beautiful lacework of reticulum fibers to confirm the diagnosis of myeloid fibrosis. In keeping with what we have seen in the spleen, we have to accept the diagnosis of myeloid metaplasia and myeloid fibrosis. Hemosiderosis of the bone marrow with deposition of iron in endothelial elements was also noted.

Pulmonary changes were not significant. Chronic bronchitis and emphysema were present which however did not seem to have contributed very much to the illness in this man. Histologically, an accumulation and thickening of alveolar septa was noted.

The heart was normal in size, weighing 260 grams. It was somewhat brown in color and quite dilated but there were no valvular changes. The myocardium on low power inspection looked quite normal but with iron stains we saw quite surprisingly large amounts of iron deposited in the heart muscle fibers, primarily around the nucleus. In addition to the iron pigment, a brown granular, non-iron containing pigment, probably hemofuscin, was deposited. This characterizes hemochromatosis. Since we suspected the presence of the disease, we looked at the parenchymal iron distribution in contrast to that in the reticuloendothelial system which can result from excess iron storage from blood transfusions. Iron was present in the cells of the thyroid follicle (Fig. 5). In the skin no pigmentation was found. The clinicians told us of the peculiar hue that was present in the patient and the iron stain of the adnexa next to the skin shows the excess iron in the vessel as well as in the sweat glands to confirm the diagnosis of hemochromatosis. The lymph nodes were not as well preserved as those obtained at surgery but we convinced ourselves that excessive iron was deposited in the lymph nodes at the time of death in contrast to five years before at surgery. That means that within five years large amounts of iron had accumulated.

The kidneys looked anemic and had a slight green hue. Microscopic examination revealed bile pigment in the distal convoluted tubules, pointing to a nephrosis in addition to iron deposition in the same tubules. Enlargement of the prostate was confirmed as benign and nodular hyperplasia with atrophy of the testes.

At the site of subtotal gastrectomy, only a very small amount of stomach was left with no gross alterations. The duodenum was quite normal although the iron stains showed a very large amount of iron as is known to occur in hemochromatosis. Except for dilatation, which probably is related to the paralytic ileus, and a brown discoloration, there were no anatomic changes which possibly could be considered a cause of a secondary malabsorption syndrome.

The intestinal mucosa was normal except that it contained some brown pig-

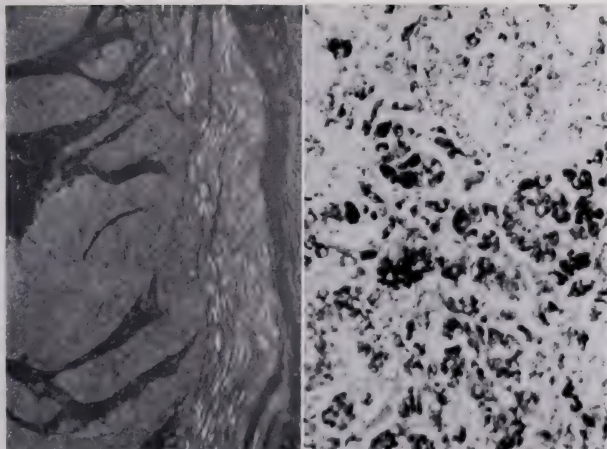


FIG. 6. Fluorescence photomicrograph showing bright fluorescence of pigment in the muscularis ($\times 63$).

FIG. 7. Iron deposition in the islets of Langerhans, the acini, ducts and connective tissue of the pancreas (iron stain $\times 120$).

ment. There was no increase in follicles and no gross changes. In the deeper layers we saw increased cellularity, normal spacing of villi, and normal architecture except for the presence of large amounts of iron, characteristic of hemochromatosis. The only significant finding in the outer layer of the muscularis was a large amount of a granular pigment which was very highly fluorescent (Fig. 6). This has been described as characteristically occurring in several conditions but only rarely in the tremendous amounts. Dr. Adlersberg described it in sprue and it also occurs in exudative or protein losing enteropathy. Here was the first significant pathological finding of this condition, namely, the sprue-like pigment in the outer layer of the small intestine.

The pancreas remaining was quite different from that removed some five years before. Accumulation of large amounts of fiber and excessive amounts of iron in the islands and in the interstitial tissue were found (Fig. 7).

The liver was smaller than normal and somewhat reduced in consistency. The jaundice was not related to any extrahepatic lesion since the extrahepatic ducts were normal. On the cut surface the architecture was not very much altered. Microscopically we saw very markedly pigmented portal tracts with some cellular infiltration around the central zones. Increasing amounts of iron were deposited from the central zone to the lobular periphery, characteristic of hemochromatosis, and the iron was deposited, as we would have expected, in the parenchymal liver cells as well as in reticulum cells (Fig. 8). Where the liver cells disintegrated,

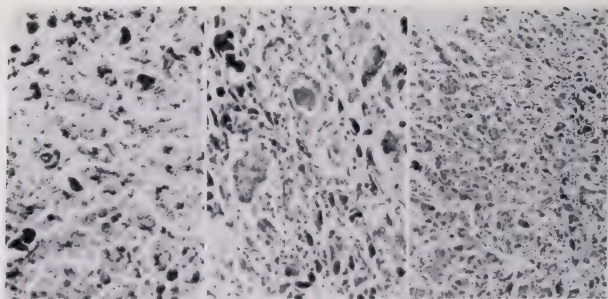


FIG. 8. Iron deposition in hepatic parenchymal cells and in Kupfer cells, especially near zones of necrosis (iron stain $\times 120$).

FIG. 9. Section of liver showing severe cholestasis with microcalculi in proliferated ductule. Giant cell formation of liver cells is seen (H & E $\times 240$).

FIG. 10. Large area of collapse in liver extending into several lobules (H & E $\times 63$).

the Kupffer cells became heavily laden with iron and iron deposition extended into the portal tracts causing a severe degree of fibrosis, the beginning of cirrhosis associated with hemochromatosis. A few features did not fit the diagnosis of hemochromatosis. Very severe bile stasis was present with formation of giant cells and marked cellular infiltration (Fig. 9). Indeed, throughout the entire parenchyma we found accumulations of scavenger cells, most of them iron containing and forming follicles in areas of collapse (Fig. 10). This does not occur in hemochromatosis. In short, we can confirm Dr. Adlersberg's diagnosis. We were dealing with viral hepatitis complicating hemochromatosis. A last finding was obstruction of portal vein branches as well as old fibrous bands around the veins. In the hepatic vein branches, there was also evidence of pre-existing hepatic thrombosis.

We were dealing with protein-losing gastroenteropathy (2, 3, 6). After removal of the stomach, the manifestation of the protein-losing gastroenteropathy did not subside but progressed. Possibly the hypertrophic gastritis was not the cause of the protein loss but rather a response to a pre-existing exudative status of the entire intestinal tract.

We have to assume the presence of a peculiar disease, a form of sprue, because of the presence of intestinal pigment, which could also have been the result of malabsorption rather than the cause. I would therefore postulate that the basic disease was protein-losing gastroenteropathy, with low serum albumin, low cholesterol, and anasarca and emaciation. Whether the anemia was macrocytic, we do not know. It could have been the macrocytic anemia following gastrectomy or part of the preexisting disturbance of sprue.

The patient undoubtedly has myeloid metaplasia and I do not know whether the myeloid metaplasia is a response to the deficiency and whether myeloid metaplasia produces, in a way, the sprue-like condition.

Dr. Victor Herbert suggested a third possibility, that it was just coincidence.

Anyway, with the stomach, pancreas and spleen removed, the patient had malabsorption emaciation, anasarca, fatty diarrhea, anemia, murmurs and osteoporosis. He had many blood transfusions and in the presence of myeloid metaplasia with increased iron absorption, the iron was transferred into the parenchymal cells, causing hemochromatosis. In order to make things even more interesting, the patient developed viral hepatitis with lack of taste for cigarettes. The ileus-like picture is not clear to me and I wonder whether the patient had some primary damage of intestinal muscles.

Dr. Victor Herbert:§ I have to go along with the possibility that this patient had two unrelated conditions; one, myeloid metaplasia of unknown etiology, and the other, sprue, perhaps secondary, possibly primary, which had produced much of the picture which appeared after gastrectomy. The picture, while the stomach was in, could be explained by the hypertrophic rugae in the stomach. In the early days of liver therapy for pernicious anemia, it was discovered that a fair percentage of patients did not respond to liver, although vitamin B₁₂ was in their diets. It would seem if some deficiency had been present a long time and the marrow ceased to respond to vitamin B₁₂. This category is known as megaloblastic anemia, refractory to B₁₂ and folic acid. This individual could fall into that category because he has had protracted B₁₂ deficiency after his gastrectomy and in spite of B₁₂ and folic acid therapy.

How can one relate the myeloid metaplasia with vitamin B₁₂ and folic acid deficiency which we can explain on the basis of his gastrectomy and perhaps also on the basis of his malabsorption which could have existed prior to his gastrectomy?

Did this patient have macrocytosis before he had his gastrectomy? Not knowing that, we cannot say, but there are any number of reports in the literature attempting to tie together vitamin B₁₂ deficiency with polycythemia vera and with leukemia. Polycythemia vera and leukemia have been related to myeloid metaplasia as a single entity. If this turns out to be so, and if there is in fact a relationship between polycythemia vera and pernicious anemia, and between leukemia and pernicious anemia, one can see a relationship which is intermediate. It is a tenuous relationship and no one has ever established definitively that there is any relationship between polycythemia or leukemia and pernicious anemia, although much has been written on the subject.

To me, the jejunal biopsy rules out sprue. I think this is all we can say by way of attempting to link together these phenomena. In the final analysis we have to say, as we said in the beginning, that this patient had two unrelated conditions: myeloid metaplasia and sprue, primary and or secondary. With respect to the hemochromatosis, this could be due in part or completely to a vitamin B₁₂ deficiency, which can lead to pure hemochromatosis.

Dr. Adlersberg: It is a most unusual case, and perhaps a few final remarks may be in order concerning his sprue. I also believe that primary sprue is out of the question because of several considerations which I presented before, and because of the normal jejunal biopsy. On the other hand, Dr. Popper did not

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find any abnormalities in the small bowel such as Whipple's disease or amyloidosis. Several cases published as exudative enteropathies with the picture of sprue did not have the typical features of sprue. The only feature which was seen in all was the peculiar pigment accumulation in the muscularis mucosae of the bowel. A few years ago, we thought this pigment was hemofuscin, but many stains were done in order to rule out the possibility that this was perhaps "ceroid pigment" which was found in vitamin E deficiency. These cases with exudative enteropathy have peculiar clinical picture of malabsorption which do not fit too well within the typical outline of this condition. It was interesting that this patient had marked fibrosis of the pancreas. In a number of cases of sprue, we saw interstitial pancreatic fibrosis.

Dr. Popper: The large amount of iron might explain it here.

Dr. Adlersberg: It also has been interpreted on the basis of prolonged nutritional deficiency that these people suffer from. I do not believe that we have ever seen another case with sprue and myeloid metaplasia, so I would believe that this is, if at all, a rare feature of sprue. I would agree with Dr. Herbert and Dr. Popper that this is rather an independent disorder. I would like to ask Dr. Popper about the relationship of hemochromatosis to malabsorption. We had one or two patients who showed malabsorption in the end stages of hemochromatosis.

Dr. Popper: Any type of malabsorption disease will favor the absorption of iron in turn, so obviously if there is a tendency for hemochromatosis, in view of the myeloid metaplasia and vitamin B₁₂ deficiency, it is accentuated in the presence of whatever the malabsorption syndrome is. In closing, I think that we are dealing with what I would call primary sprue not in the sense of an absorption defect but in the sense of a losing defect. It is a sprue-like picture resulting from a protein-losing gastroenteropathy.

Final Diagnosis: PROTEIN-LOSING ENTEROPATHY WITH GIANT GASTRIC RUGAE NOT IMPROVED BY GASTRECTOMY. VIRAL HEPATITIS. HEMOCHROMATOSIS. MYELOID METAPLASIA.

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Radiological Notes

Neuroradiology

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CASE NO. 108

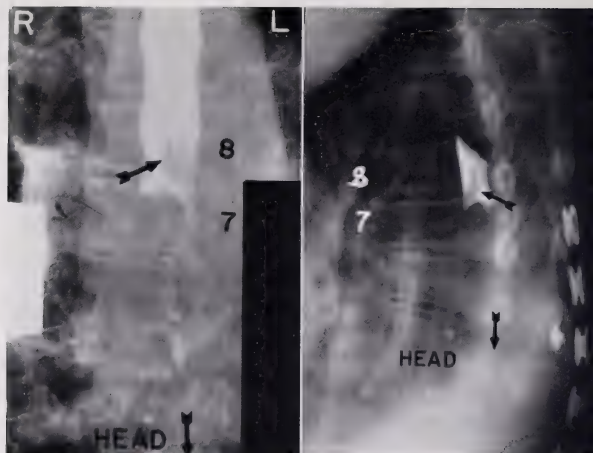
A 65 year old female was admitted with a 13 month history of difficulty in walking. The first complaint was stiffness in the right foot which resulted in her inability to lift that leg. A short time later this was followed by similar difficulties with the left leg so that walking became quite difficult.

Neurological examination on admission showed a paresis more marked in the right lower extremity. Deep reflexes were increased somewhat more on the right side. Babinski signs were present bilaterally. Vibration sense was lost below the 9th thoracic segment. Position sense was lost in all of the toes, and pinprick sensation was diminished on the left side below the 10th thoracic level with a less pronounced sensory deficit on the right side. Lumbar puncture including manometric studies appeared to be within normal limits. Spinal fluid protein was 130 mgm per 100 cc.

Roentgen examination of the dorso-lumbar spine was not remarkable. Pantopaque myelography was then performed via the lumbar route. This revealed an incomplete block (Figs. 1A & 1B) to the cephalad flow of the opaque material at the level of the lower margin of the 7th thoracic vertebra. A thin column of material passed by the obstructing lesion on its left side and anteriorly. At the site of block, there was a sharply demarcated crescentic border to the opaque column, that is, a smooth cap. The spinal cord seen faintly through the opaque material distal to the filling defect was displaced towards the left and anteriorly. The findings were typical of an extra-medullary intradural mass arising on the right side and posteriorly. Sufficient opaque material went by the lesion to permit visualization of the proximal border of the defect when the patient was subsequently placed in the erect position (Fig. 1C). The configuration of the surface of the filling defect was identical proximally to its appearance distally.

Laminectomy was performed and a typical meningioma was removed along with its dural attachment. Post-operatively, the patient did quite well. Two months after the operation, there was residual minimal weakness of the flexors of the right hip and no sensory deficit. She was able to walk quite well with the aid of a cane.

A spinal cord tumor in the dorsal region in a female over the age of 50 turns out to be a meningioma in the majority of cases. Myelographic features demonstrated in this case are quite classical and include the demonstration of a smooth, sharply demarcated filling defect which displaces the cord. In some cases, there



Case 108, Fig. 1A. Spot film taken during the course of pantopaque myelography with the head lowered shows an incomplete block to the cephalad flow of the opaque material at the level of the lower border of the 7th thoracic vertebra. The distal margin of the filling defect is sharply outlined and crescentic in configuration. The spinal cord (arrow) is displaced towards the left. A small amount of opaque material flowed around the left side of the tumor mass.

Case 108, Fig. 1B. A lateral view with the head lowered, taken at the same time as Fig. 1A, with a horizontal beam also demonstrates the sharply demarcated crescentic cap to the opaque material slightly cephalad to the lower margin of the body of the 7th thoracic vertebra. The cord (arrow) is displaced forward. The apparently oblique sharp line of the upper, actually the caudal, surface of the pantopaque column is a fluid level.

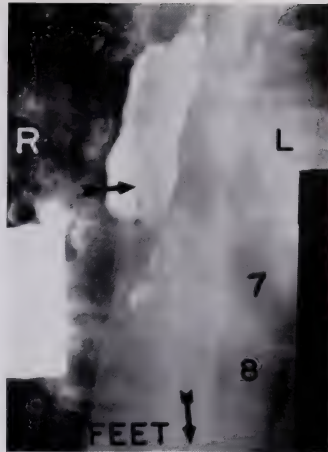
is widening of the interpedicular distance with erosion of one or both pedicles at the level of the tumor. This latter finding is more common with neurofibromatous tumors than with meningiomas.

Final Diagnosis: THORACIC MENINGIOMA.

CASE NO. 109

A 38 year old white female was admitted because of progressive difficulty in walking of one years' duration. The symptoms started with paresthesias in all the toes. This was followed by a loss of temperature sensation in the lower extremities. There was no bladder or bowel disturbance except for frequency in urination. One year previously, she had been told that she had a gastric ulcer.

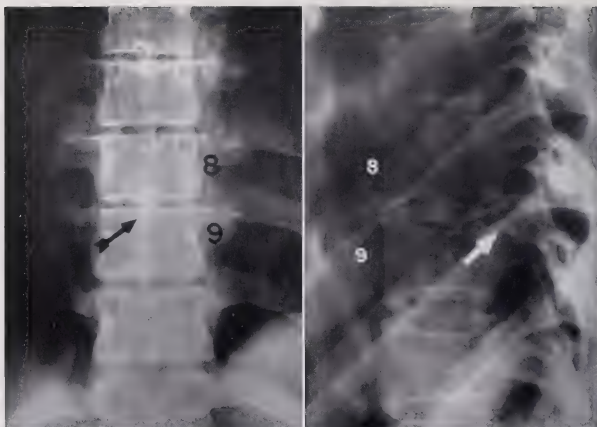
Case 108, Fig. 1C. Spot film taken during the course of myelography with the head elevated shows an incomplete block to the caudal flow of the opaque material at the lower margin of the 6th thoracic vertebra. The appearance of the superior or proximal margin of the filling defect is similar to the inferior margin demonstrated in Fig. 1A. The spinal cord above the tumor mass is also deviated toward the left (arrow). The length of the tumor is about the length of the body of the 7th thoracic vertebra. For simplicity, the film is presented as if the body was vertical, that is, at an angle of 90° with the horizontal plane. In actual fact, the plane of the body formed about an angle of 65° with the floor.



Physical examination on admission was not contributory except for the neurological findings. There was a loss of sensation for pain, touch, temperature and vibration bilaterally up to the level of the 10th thoracic segment. The tendon reflexes were increased in both lower extremities and bilateral Babinski responses were noted. Lumbar puncture showed clear spinal fluid with a protein content of 60 mgm per 100 cc. Manometric studies demonstrated a partial block.

Roentgen examination of the thoracic spine showed moderate narrowing of the intervertebral space between the 8th and 9th dorsal vertebrae with punctate calcific deposits within the nucleus pulposus. Of greater interest, however, was the fact that a larger ovoid rather homogeneous area of calcification was noted within the spinal canal immediately posterior to and adjacent to the posterior margin of the calcified nucleus pulposus (Figs. 1A & 1B). Pantopaque myelography via the lumbar route (Figs. 2A & 2B) demonstrated a complete block to the cephalad flow of the opaque material at the level of the intraspinal calcification or rather a short distance caudal to it. In the postero-anterior projection (Fig. 2A), the pantopaque column at the site of block formed a slightly irregular cap which paralleled the superior border of the calcification. The spinal cord did not appear to be displaced. In the lateral projection, the pantopaque column at the site of the calcification also paralleled the calcification which produced an indentation on its anterior aspect. The cord was displaced backwards.

At laminectomy, a calcified extruded disc was removed extradurally. This



Case 109, Fig. 1A. The dorsal spine shows narrowing of the intervertebral space between the 8th and 9th thoracic bodies. There is a stippled calcification in the middle of this intervertebral space. In addition, however, extending equally above and below the space, an ovoid calcification (arrow) is seen which has a more homogeneous density.

Case 109, Fig. 1B. A lateral view of the dorsal spine shows the ovoid calcification (arrow) to extend into the spinal canal at the level of the intervertebral space between the 8th and 9th thoracic bodies.

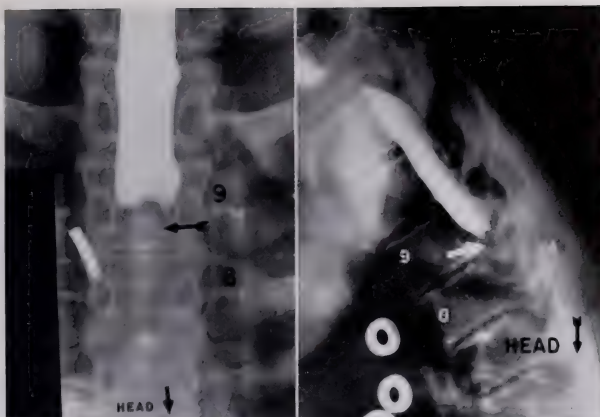
was quite hard and had to be ronguered away from the bone. On histological examination, the material showed bone and cartilage.

The presence of an area of discrete calcification, that is, a calcified "mass" within the spinal canal is not common and suggests either psammomatous calcification in a meningioma or calcification in extruded intravertebral disc material. In the case presented, the homogeneity of the calcification and the fact that there was associated calcification of the nucleus pulposus with narrowing of the intervertebral space permitted the correct diagnosis. The extra-dural location of the mass with irregular outline of the pantopaque column at the site of block supported the diagnosis of herniated disc. Herniation at this level into the spinal canal is quite unusual and is particularly striking in as young a person as this one. There was no roentgen evidence of old fracture or dislocation and there was no history of trauma obtainable.

Final Diagnosis: EXTRUDED CALCIFIED THORACIC DISC.

CASE NO. 110

A 26 year old female was admitted to this hospital in 1954 with a history of progressive weakness of her right leg and foot since the age of 3 years. A diag-



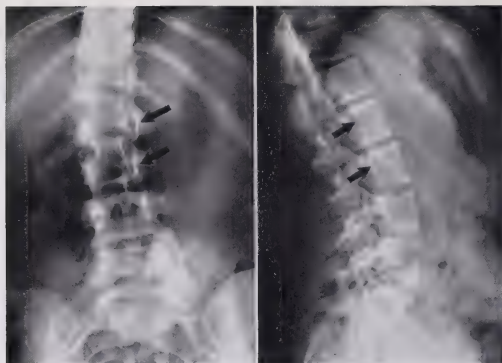
Case 109, Fig. 2A. Pantopaque myelography with a 70° inclination, head lowered, shows practically complete block to the cephalad flow of the opaque material a short distance caudal to the calcified area (arrow). The cap is rather transverse and somewhat irregular in configuration. There is a soft tissue gap of about 2 mm between the end of the opaque column and the calcified area. The cord is faintly seen within the opaque material and is not displaced in this postero-anterior or frontal projection.

Case 109, Fig. 2B. A lateral view taken at the same time as Fig. 2A demonstrates that the pantopaque column is indented anteriorly (arrow) in relationship to the calcification. The irregularity of the "cap" is again noted.

nosis of paralytic poliomyelitis was made. Two years before admission, during an upper respiratory infection, she developed increasing weakness in the right leg and numbness and pain in the right knee. The right leg would "tighten, quiver and shake". These episodes lasted from a few minutes to an hour. At the time of admission, the patient complained of marked weakness particularly in the right leg and required a cane to walk. She also stated that her leg felt cold. There were no bowel or bladder disturbances.

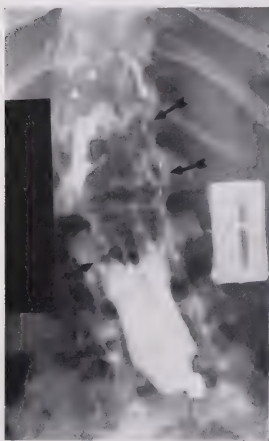
Physical examination on admission was negative except for neurological findings. There was weakness of all of the muscle groups of the right foot and of the flexors of the right knee and the abductors of the right thigh. The right lower leg was cold and atrophic. It also showed diminished sensation to pain. Position sense was defective in the right foot and in the right toes. A spina bifida between L4 and L5 was palpable and a vascular discoloration of the skin was noted in the same area.

Examination of the lumbar spine (Figs. 1A & 1B) confirmed the presence of a spina bifida of the fourth lumbar body. There was a transitional lumbo-sacral



Case 110, Fig. 1A. Antero-posterior view of the lumbar spine shows a rather marked scoliosis convexity towards the right. The interpedicular spaces are markedly widened particularly at the 1st and 2nd lumbar segments. The pedicles on the left side (arrows) are markedly thin. A spina bifida of the fourth lumbar segment is present and there is a transitional lumbo-sacral vertebra.

Case 110, Fig. 1B. Lateral view of the dorsal spine shows marked excavation of the posterior aspects of the upper lumbar vertebral segments (arrows).



Case 110, Fig. 2. Pantopaque myelography through the lumbar route shows an incomplete obstruction to the cephalad flow of the opaque material at the level of the mid-portion of the second lumbar body (lower right arrow). There is a crescentic cap at the site of block. A small amount of material traversed the area of block and partially outlined the upper aspect of the mass which extended to the level of the 12th dorsal vertebra. Marked widening of the spinal canal particularly to the left causing pressure on the pedicles (arrows) is clearly delineated.

segment below this region also with incomplete laminae. A fairly marked scoliosis with little rotation was noted in the upper lumbar region. The convexity was towards the right. The configuration of the pedicles was therefore somewhat difficult to delineate but it was obvious that the pedicles on the left side of the 12th thoracic and the 1st and 2nd lumbar vertebral segments were markedly narrowed as a result of pressure on their medial aspect. As a result, the interpedicular spaces were remarkably widened. At the same vertebral levels, there was also marked excavation of the posterior aspects of the vertebral bodies indicating symmetrical antero-posterior as well as lateral widening of the spinal canal. Lumbar puncture showed clear spinal fluid with a protein content of 20 mgm per 100 cc. Manometric studies showed evidence of block. Pantopaque introduced through the lumbar route showed incomplete block to the cephalad flow of the opaque material which outlined a crescentic cap caudally at the level of the mid-portion of the body of the 2nd lumbar vertebral segment (Fig. 2). Above this, the spinal canal was obviously markedly widened particularly on the left by an



Case 110, Fig. 3. Examination of the lumbar spine five years after laminectomy shows some restitution of the normal configuration of the pedicles on the left side of the 1st and 2nd lumbar segments (arrows). No other remarkable change has occurred.



Case 110, Fig. 4. Repeat myelography shows no evidence of any block or any filling defect at the site of the previous tumor. The subarachnoid space bulges less (arrows) than was seen at the original examination.

ovoid filling defect the superior margin of which appeared to extend as high as the level of the 12th thoracic segment.

Laminectomy was performed from the 11th thoracic vertebra to the 3rd lumbar vertebra. A markedly dilated spinal canal was found which was occupied by an encapsulated intradural tumor. The tumor appeared to extend downwards around the conus medullaris. All of the free capsule and contents were removed except for the portion which involved the conus. The tumor was reported as an epidermoid.

Post-operatively, the course was uneventful and there appeared to be some recovery in motor function at the time of discharge three weeks later. She was readmitted in 1959 with increasing difficulty in walking and pain in the right lower extremity. She also complained of pain and numbness in the left lower extremity as well as difficulty in micturition. Examination at this time showed diminished power in both lower extremities. Re-examination of the lumbar spine (Fig. 3) showed no remarkable change in the interpedicular distances but the pedicles on the left side that previously were markedly narrowed had a more normal configuration. Lumbar puncture showed no evidence of block and repeat pantopaque myelography (Fig. 4) showed no evidence of obstruction to the cephalad flow of the opaque material or evidence of a filling defect.

This case is of interest because of the fact that for many years, the diagnosis of an intraspinal tumor was overlooked and was not considered until sensory changes necessitated reevaluation.

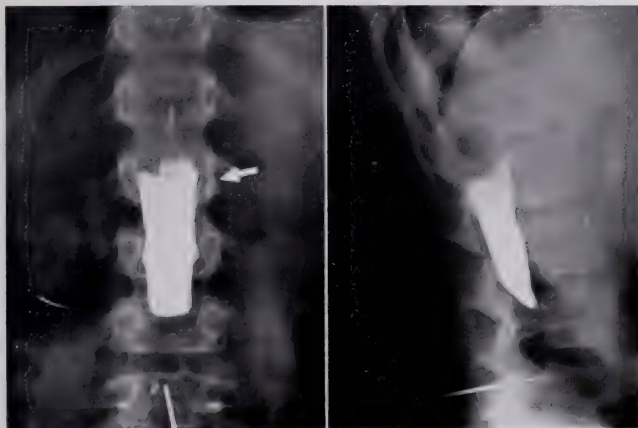
Final Diagnosis: CAUDA EQUINA EPIDERMOID.

CASE NO. 111

This was the first admission of an 11 year old boy with the chief complaint of pain in the right hip area. Pain started four years prior to admission and was

originally intermittent, returning particularly during the hay fever season when the patient did a good deal of sneezing. The pain was maximum in the region of the hip but also involved the outer aspects of the thigh and leg. About a month prior to admission, during the hay fever season, pain became quite sharp and severe and the child was unable to move his right lower extremity for a period of about 20 minutes. By the next morning, however, he was able to move the leg quite well although pain persisted. Coughing and rapid motions also caused exacerbations of pain. He also noted recently that, when going down steps, he had to go slowly to prevent falling.

Examination on admission showed moderate weakness of the flexors of the right hip. When the patient was at rest in bed, the right leg was kept externally rotated. There was no local spinal tenderness. The deep tendon reflexes were active. There were no pathological reflexes or other positive neurological findings.



Case 111, Fig. 1A. Pantopaque myelography with the head tilted downwards to about 60° shows complete obstruction to the cephalad flow of the material at the level of the body of the 2nd lumbar vertebra. The cap is rather smooth and crescentic although small serrations are present. The pedicle on the left side at this level shows marked thinning (arrow). The interpedicular distance at the 1st lumbar segment measured 28 mm; 26 mm at the 1st lumbar segment, 23 mm at the 12th dorsal segment and 22 mm at the 3rd lumbar segment.

Case 111, Fig. 1B. Lateral view taken at the same time as Fig. 1A shows that the defect occupies the entire spinal canal. A small trickle of opaque material anteriorly occupies the indentations on the posterior aspects of the vertebral bodies.

Roentgen examination of the dorso-lumbar spine showed that the interpedicular distances at the 1st and 2nd lumbar levels were increased. The pedicles on the left side of these vertebrae were flattened and thinned. The interpedicular distance at the 1st lumbar level exceeded the maximum for this age group by about 3 mm. The dorsal aspect of the body of the 1st lumbar vertebra showed an anterior convex indentation. Lumbar puncture performed between the 3rd and 4th lumbar vertebrae showed a complete block. This was confirmed at myelography (Figs. 1A & 1B) which also demonstrated that the subarachnoid space was markedly widened in both the transverse and sagittal directions with a somewhat irregular capping of the opaque material at the level of the mid-portion of the body of the 2nd lumbar vertebra. The roentgen diagnosis was that of an intradural tumor. The possibility of an intramedullary expanding lesion was not considered since the lower end of the lumbar cord is ordinarily at a higher level than the site of block demonstrated. Since no opaque material passed the site of block, it was not possible to visualize the upper limit of the defect. At laminectomy, the dura was opened at the 1st and 2nd lumbar segments and a 4 x 3 x 3 cm encapsulated epidermoid tumor was found in the ventral portion of the cauda equina surrounded by numerous nerve roots. The tumor was completely removed as far as could be determined. Only the root of the 2nd lumbar vertebra on the right side, which was intimately adherent to the capsule, had to be resected. The patient was discharged nine days post-operatively with residual minimal weakness of the right hip, flexors, and internal rotators, and minimal hypalgesia of the lateral aspect of the right thigh. Follow-up examination of this patient about a year after the operation showed that there was absolutely no disability and the child participates actively in all types of athletic competition. He has no complaints of pain.

In contrast to the previous case, this is a example of an epidermoid of the cauda equina in which early removal permitted complete restoration of function.

Final Diagnosis: EPIDERMOID OF THE CAUDA EQUINA.

CASE NO. 112

A 72 year old female was admitted with a history of sudden loss of consciousness lasting 10 or 15 minutes which had occurred one month prior to admission. After regaining consciousness, she was unable to speak and was paralyzed on the right side of the body. There was no previous history of convulsions, paresthesias, speech difficulty or syncope. For about four years, she had complained of periodic headaches.

Neurological examination revealed a right flaccid hemiplegia and marked aphasia. There was a right-sided hypesthesia and a right central facial weakness. Tendon reflexes on the right side were absent and a Babinski sign was present on the right. General physical examination was negative except for auricular fibrillation.

Lumbar puncture revealed an initial pressure of 90 mm of water. Spinal fluid was crystal clear. Protein content of the fluid was 54 mgm per 100 cc. Serology was negative.



Case 112, Fig. 1A. Antero-posterior projection during the early arterial phase of the carotid angiogram shows obstruction (arrow) to the flow of contrast material in one of the two main branches of the middle cerebral artery about half-inch distal to its origin from the trunk of the middle cerebral artery. The anterior cerebral artery is in the mid-line. There is no evidence of displacement of the other vessels visualized.

Simple films of the skull were within normal limits. Left carotid percutaneous arteriogram showed a sudden block to the flow of the opaque material in one of the two main branches of the middle cerebral artery (Figs. 1A & 1B). In the lateral view (Fig. 1C), it was evident that the temporal branch of the middle cerebral artery was filled but that the parietal branch could not be seen. In the later phases of the arteriogram, a network of small vessels in the parietal area was demonstrated apparently as the result of collateral circulation from the anterior cerebral artery (Fig. 1B) and perhaps also from the temporal branch of the middle cerebral artery. The anterior cerebral artery and the internal cerebral vein were well visualized and not displaced in either the frontal or lateral projections. The internal carotid artery and the carotid siphon were slightly irregular in contour suggesting the presence of arteriosclerotic plaques.

In a patient with auricular fibrillation, the possibility of embolization cannot be excluded although, in view of the age, thrombosis on an arteriosclerotic basis



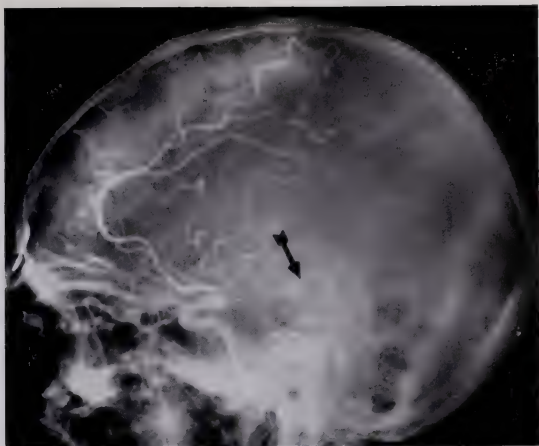
Case 112, Fig. 1B. In a later phase of the angiogram, the obstruction persists (lowermost arrow). Numerous vessels (arrows) are seen in the parietal area joining the pericallosal branches of the anterior cerebral artery to the temporal branch of the middle cerebral artery.

seems an equally if not more likely possibility. The diagnosis of vascular occlusion is based on abrupt termination of the opaque column which persists and failure to visualize the vessels beyond the site of obstruction in normal sequence. The absence of displacement of any of the arteries or veins indicates no associated intracerebral hematoma or marked cerebral edema. At the present time, carotid angiography in a case such as this serves to exclude a mass lesion. In the future, it may be possible to base more specific therapy on the anatomical and physiological features which can be well demonstrated by this method.

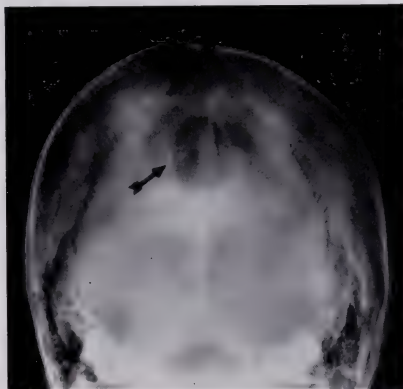
Final Diagnosis: OCCLUSION OF THE PARIETAL BRANCH OF THE MIDDLE CEREBRAL ARTERY.

CASE NO. 113

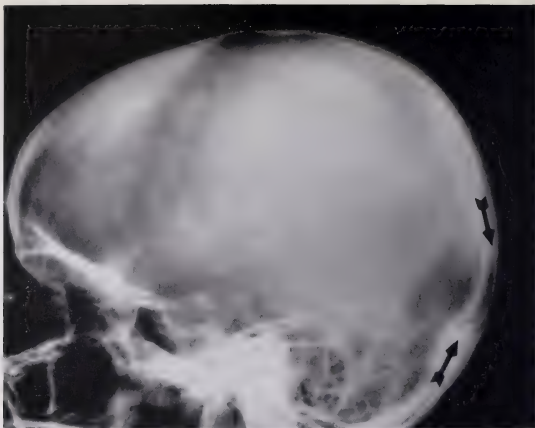
This was the first admission of a 44 year old woman with a long history of headaches most pronounced in the left occipital region. The severity of the headaches had been increasing over the last four or five years. About a year and



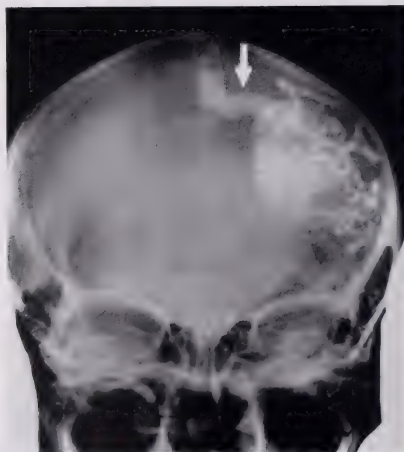
Case 112, Fig. 1C. Lateral view in the early phase of the angiogram shows filling of the temporal artery but failure to visualize the parietal branches of the middle cerebral artery. The ascending fronto-parietal branches of the middle cerebral artery are well filled. The carotid siphon is irregular in contour indicating arteriosclerotic changes.



Case 113, Fig. 1A. Fronto-occipital or Towne's projection of the skull shows a sharply demarcated, rounded, honeycombed bony defect (arrow) in the superior portion of the occipital bone in the mid-line.



Case 113, Fig. 1B. In the lateral projection, the lesion (arrows) shows a similar appearance. It is somewhat obscured by the overlapping normal diploic structure. The lesion follows the curvature of the calvarium.



Case 113, Fig. 2. Percutaneous left carotid angiography shows that practically all of the opaque material enters the middle cerebral artery which is dilated and tortuous with many large branches supplying a hypervascularized area in the parieto-occipital region. Numerous sinusoidal intertwining communicating vessels, both arterial and venous, are present within this area and there is a huge draining vein (arrow) which enters the superior longitudinal sinus.

a half before admission, she was admitted to another hospital because of an episode of sudden loss of consciousness. She remained unconscious for several days and then gradually improved. During this episode, she developed severe visual disturbances. The diagnosis of an arteriovenous anomaly was made presumably after angiography. After discharge, vision on the right side improved although some difficulty remained and headaches became steadily worse.

Examination on admission revealed a right homonymous hemianopsia more marked inferiorly than superiorly. Right lower facial asymmetry was present. The remainder of the neurological examination was negative. Electroencephalogram showed no abnormality. Examination of the skull (Figs. 1A & 1B) showed a sharply demarcated, honeycombed oval lesion in the mid-line of the occipital bone typical of a hemangioma. Left carotid angiogram showed no filling of the anterior cerebral artery. The middle cerebral artery was well filled, markedly enlarged and tortuous. Numerous dilated vessels from the middle cerebral artery supplied a large arteriovenous anomaly in the parieto-occipital region with rapid visualization of a huge draining vein extending into the superior sagittal sinus (Fig. 2). Several days later, right percutaneous carotid angiography was performed. The vessels on the right side did not appear to be remarkable and there was no shift of the anterior cerebral artery from the mid-line. The malformation in the left parieto-occipital region was not visualized on the right angiogram until contralateral compression was made of the left carotid artery. The patient tolerated these procedures well and her neurological status remained unchanged. It was decided that the patient could be followed in the Out Patient Department until a more serious disturbance in functioning occurred or until bleeding recurred. The therapeutic problem in a case such as this is formidable and clearly indicated by angiographic studies which outline the vessels supplying and draining the anomaly. As demonstrated in this patient, occlusion of the carotid artery on the side of the lesion does not prevent filling which will then occur from the opposite side. The association of a hemangioma of the skull with an intracranial arteriovenous anomaly is rare and may be coincidental.

Final Diagnosis: ARTERIOVENOUS ANOMALY OF THE BRAIN PLUS HEMANGIOMA OF THE SKULL.

Surgical Techniques

2. TECHNIQUE OF REPAIR OF ESOPHAGEAL HIATUS HERNIA

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The technique of repair of esophageal hiatus hernia is presented in the following series of illustrations. Too often, these hernias are repaired without a true knowledge of the surgical anatomy. We have tried to emphasize the important facts necessary for good repairs. The transplantation of the esophago-gastric junction below the diaphragm and its continued positioning there is essential for the disappearance of symptomatology associated with this condition.

The section on Surgical Techniques is one of a series prepared by the Department of Surgery. Some of the techniques described are original, others are of long-established application, some with modifications found useful here. The descriptions afford a concise review of techniques currently utilized at The Mount Sinai Hospital, New York.

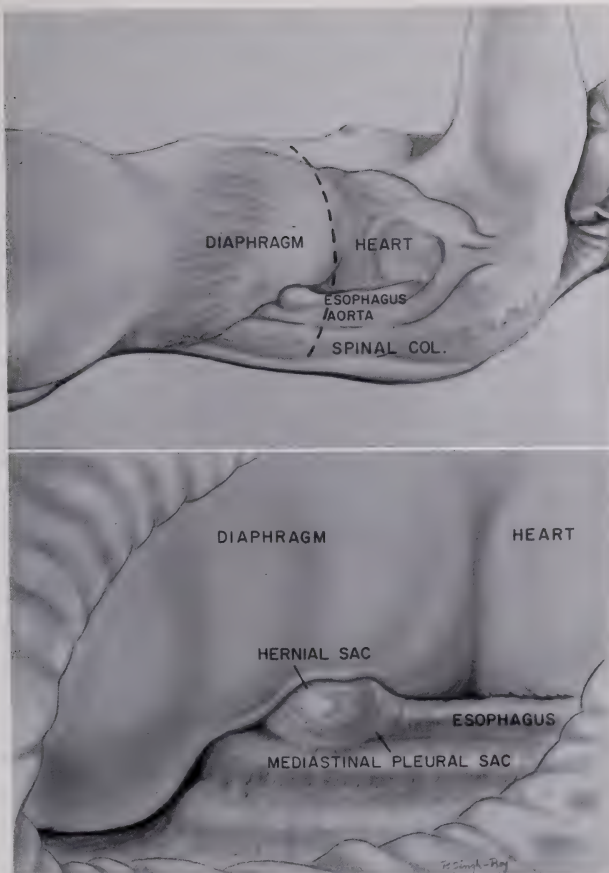


Fig. 1. Position of patient in left lateral decubitus. The incision is outlined. It is usually in the 7th or 8th intercostal space.

Fig. 2. The chest has been opened. Note the hernial sac which is seen through the mediastinal pleura.

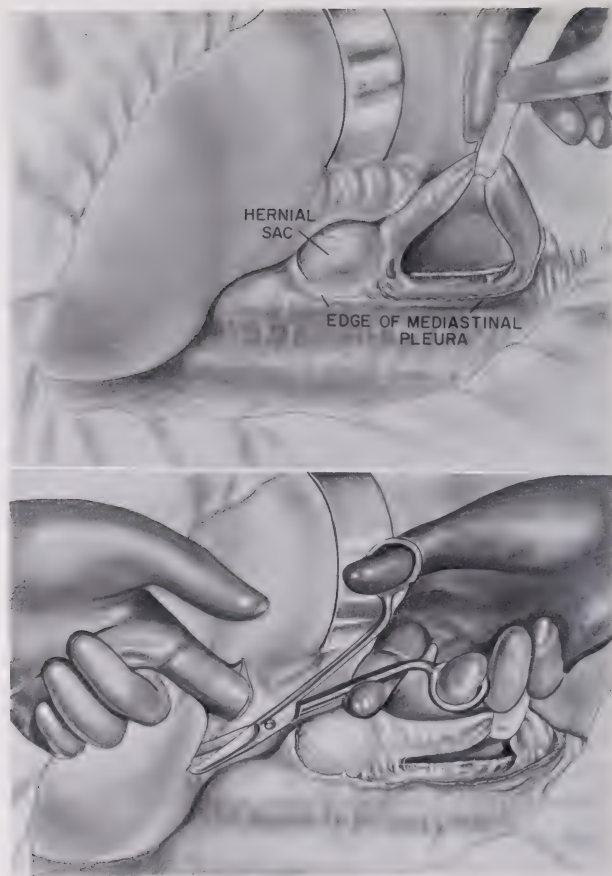


Fig. 3. The mediastinal pleura has been opened. A traction tape is placed around the esophagus and the esophagus dissected out of its bed. The hernial sac is now clearly visible at the lower end of the incision.

Fig. 4. A radial incision, avoiding the phrenic nerve or its fibers, is now made in the diaphragm. A finger can now be inserted into the sac from below.

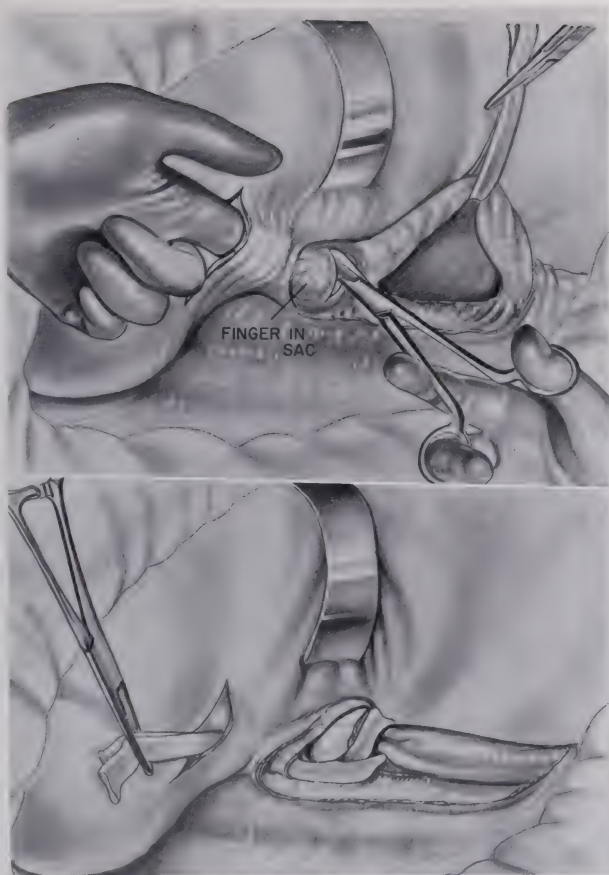


Fig. 5. The finger is inserted into the sac. The sac is now dissected away from the esophagus as it reflects on to the esophagus (phreno-esophageal ligament?)

Fig. 6. A tape is now placed around the lower end of the esophagus in the area where the sac has been reflected, and it is pulled through the incision in the diaphragm.

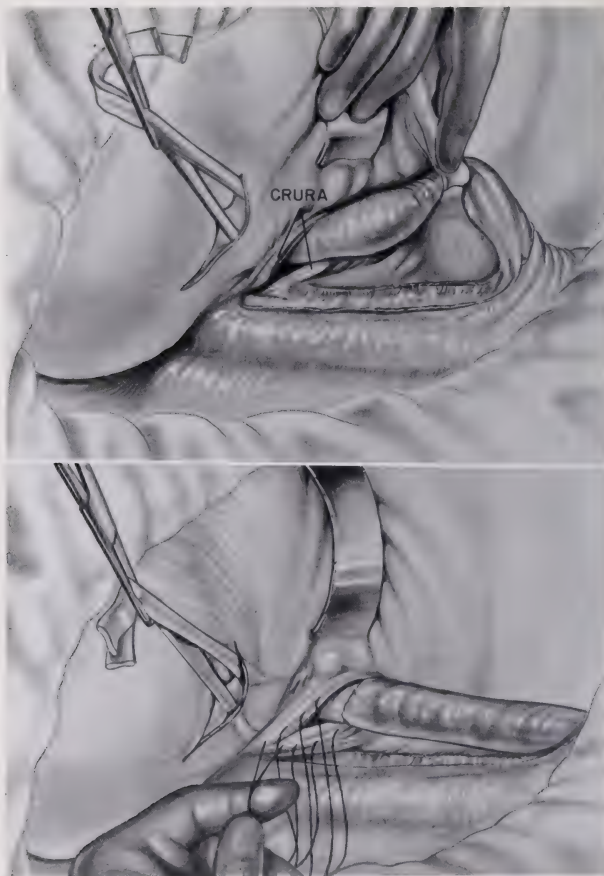


Fig. 7. Keeping traction on this tape and pulling in an anterior direction, the cardio-esophageal junction is pulled below the diaphragm. In addition, by pulling on the tape that has been placed first around the esophagus, the crura are put under tension and can be outlined clearly with minimal dissection.

Fig. 8. The crura are now approximated by 3 or 4 sutures of 2-0 silk. The juxta-esophageal suture should be placed so that the little finger only can now be inserted between the crura and the esophagus.

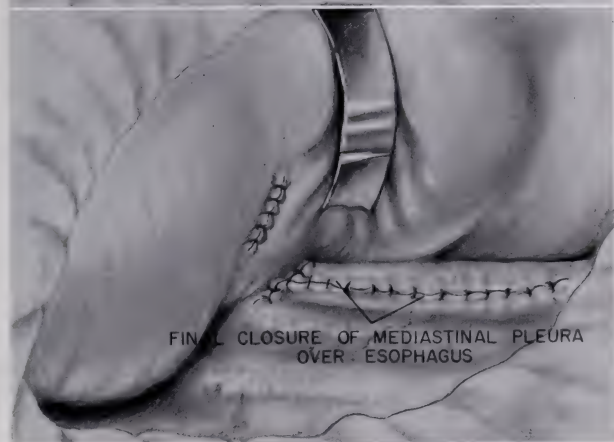
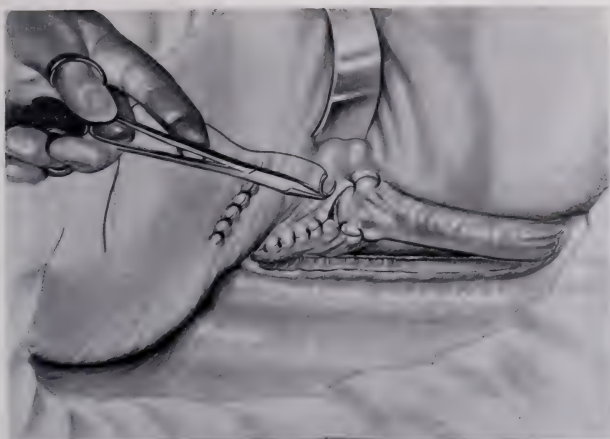


Fig. 9. Final sutures are being placed between the diaphragmatic hiatus and the lower end of the esophagus. This will fix the esophagus in its final position.

Fig. 10. The mediastinal pleura has been closed.

Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital

Effect of Calcium Loads on Tubular Function. A. Daniel Hauser, M.D., D. Polimeros, M.D. and Marvin F. Levitt, M.D. (From the Department of Medicine). Presented December 4, 1959.

Attempts were made in man to define the site of action of calcium and to determine whether the diuresis is obligated by the natriuresis or also represents diminished tubular permeability to water. Such a solute and water diuresis was compared to those produced by other diuretics in maximally hydropenic, and normal subjects. At moderate levels of solute excretion ($\text{Cosm} = 8-10 \text{ cc/min}$), slightly more water was excreted per increment of solute excretion with calcium and meralluride than after infusion of hypertonic salt and mannitol. To amplify this difference, larger hypertonic mannitol and salt loads were infused with and without the simultaneous infusions of calcium or meralluride. The latter agents similarly and substantially depressed the calculated TeH_2O 's compared to those observed after the administration of the hypertonic loads *per se*. In the combined experiments urine remained hypertonic to plasma when solute excretion approximated 40 per cent of that filtered. In water loaded, alcohol infused, normal subjects, the increment in V and cH_2O per increment in solute excretion increased most after calcium infusions, less after sodium sulfate and least with mannitol infusions. It is suggested that calcium inhibits salt reabsorption in the proximal tubule and at the ascending loop of Henle, thereby limiting medullary hypertonicity. Hypercalcemia does not seem to alter tubular permeability to water.

Electron Microscopic Studies of Renal Biopsies in Preeclampsia. Willy Mautner, M.D., Albert Altchek, M.D., Jacob Churg, M.D., and Edith Grishman, M.D. (Department of Pathology and Cell Research Laboratory.) Presented December 4, 1959 (Studies supported in part by U. S. P. H. S. Grant # A-918, National Institute of Arthritic & Metabolic Diseases, National Institutes of Health.)

Kidney biopsies were performed on patients with preeclampsia, essential hypertension, and during different stages of normal pregnancy. The tissues were studied by means of routine, thin section and electron microscopic techniques.

The glomeruli in preeclampsia were relatively bloodless and on H & E showed a moderate thickening of the capillary basement membranes. Electron microscopy showed basement membranes of normal thickness; along the endothelial side, however, there were homogeneous deposits of a somewhat less dense material, and within this there frequently were small globular deposits of a much darker, probably osmiophilic, material.

Cytologic changes included marked swelling of endothelial cells which, together with the various deposits, markedly compressed the lumens of the glomerular capillaries. There was also an increase in the size and number of the intercapillary cells. Thin sections showed that these changes were present throughout the

glomeruli rather than being restricted to the small areas selected for electron microscopy.

It is probable that these changes in part account for the bloodless appearance of the preeclamptic glomerulus; they may also be related to the reduction in renal blood flow and the decreased filtration rate encountered in these patients. The origin of the deposits and their relation to the disease process is not known. Patients with essential hypertension and normal pregnancy showed no basement membrane or cytologic alterations of this sort; on the contrary, the capillary lumens appeared to be increased in size over the normal.

The Use of Acetylcholine Induced Cardiac Arrest in Coronary Arteriography. Elliot Senderoff, M.D., Albert Welberry, Ph.D. Ephraim Donoso, M.D., and Ivan D. Baronofsky, M.D. (From the Department of Surgery.) Presented December 4, 1959.

Coronary arteriography has been successfully performed in a series of 50 dogs utilizing the technique of acetylcholine induced cardiac arrest. The method consists of introducing a cardiac catheter with a J-shaped tip into the femoral artery and passing it in a retrograde manner to the region of the ascending aorta. The catheter tip is positioned between the coronary orifices and the subclavian vessels by x-ray control. A small polyethylene catheter is then placed in the femoral vein. Both catheters are kept patent by flushing with a heparinized saline infusion. Cardiac arrest of 6 to 12 seconds duration is produced by 0.45 mgm of acetylcholine chloride per kilogram of body weight. The effect of the acetylcholine is directly related to the rapidity of its injection. While the electrocardiogram is being monitored, the acetylcholine is rapidly injected through the femoral vein catheter and flushed with the saline infusion. Cardiac arrest occurs in approximately four to eight seconds. Approximately two seconds after the arrest is noted on the electrocardiographic tracing, 30 cc of Hypaque* are rapidly delivered through the cardiac catheter by means of a hand operated pressure injector. A roentgenogram is taken at the termination of the injection while the heart is still in arrest. Regular sinus rhythm returns spontaneously following cardiac arrest. It is usually preceded by a period of atrioventricular block of varying degree. Atropine sulfate should, however, be available as a precautionary measure to immediately counteract the acetylcholine effect if so desired. This is rarely, if ever, necessary at the above dosages. Acetylcholine may be given repeatedly in the same animal once the heart reverts to normal sinus rhythm. However, once atropine sulfate has been given, the physiologic response changes.

Experiments have been performed on normal dogs, as well as animals with previous coronary artery ligation and subsequent myocardial infarctions. The method has also been used to evaluate increases in myocardial vascularity following experimental attempts to improve coronary collateral blood circulation.

A Study of the Left Colon as a Possible Replacement for Resected Esophagus. A. Robert Beck, M.D., and Ivan D. Baronofsky, M.D. (Department of Surgery.) Presented November 9, 1959.

At present, there is a need for a good method of replacing portions of the esophagus which have been resected or are congenitally absent.

Stomach, or tubes formed from stomach, segments of jejunum, skin tubes, and tubes of plastic and other inert materials have all been used in an attempt to reconstruct the esophagus. Each has distinct disadvantages. Difficulty in mobilization, inadequate blood supply, peptic esophagitis, regurgitation, multiple operations, and stricture and fistula formation have been encountered. One of the most successful methods has been the use of segments of colon for esophageal reconstruction. In most instances the right colon has been used. Colon has the advantage of being relatively resistant to gastric secretions. It is nourished by a marginal artery which, in most instances, runs uninterrupted along its entire length. (It is occasionally discontinuous on the right side.)

It is the purpose of this study to determine whether a segment of left colon of sufficient length to replace the entire esophagus can be mobilized, and to investigate the adequacy of the blood supply to this segment from the middle colic artery. Using fresh autopsy material, the entire colon, from the cecum to the sigmoid is mobilized on a pedicle containing the middle colic vessels. Each end of the mobilized colon is swung up to the neck, and measurements taken. The middle colic artery is then divided and injected, employing a modification of the technique suggested by Reiner (Reiner, L., *et al.*: Injection studies on the mesenteric arterial circulation. *Surg.*, 45: 5, 1959) using the barium-gelatin mixture described by Schlesinger (Schlesinger, M. J.: New Radiopaque Mass for Vascular Injection., *Lab. Invest.* 6: 1, 1957). The vascular supply of the colon is then clearly demonstrated on x-ray.

To date, seven specimens have been studied. In all cases, the left colon was easily mobilized, and proved to be of adequate length to reach the chin. In two instances the right colon was very difficult to mobilize because of adhesions from previous surgery (Cholecystectomy and appendectomy) and in one case was only long enough to reach the suprasternal notch. The marginal artery filled completely in all cases. Additional cases and studies will be presented.

Electrophoretic Studies on Native Mucinous Secretion from the Canine Stomach Pouch. Martin I. Horowitz, M.D., and Franklin Hollander, M.D. (Gastroenterology Research Laboratory. Presented November 9, 1959. [Supported by Grant # C288 (N.C.I., U.S.P.H.S.).])

Anacid gastric mucinous secretion obtained by the topical application of acetylcholine to canine Heidenhain pouches, was studied by chemical and electrophoretic techniques—to determine its complexity and to develop mild methods for isolation of its proteins, mucopolysaccharides, and their complexes. The secretion (ACh Mu) was separated by centrifugation into: a gel fraction (G) and a fluid fraction (Su). G was insoluble in various aqueous and organic solvents, and was solubilized only by strong urea or alkali solutions. Pretreating G by homogenization in aq. K_2CO_3 changed its consistency and rendered it suitable for electrophoresis. Zone electrophoresis of pretreated G on paper and on starch (with veronal buffer, $\Gamma/2 = 0.075$ and pH 8.6) showed six or seven protein components by staining with amido black or by a modified biuret reaction; dialyzed Su showed protein patterns on paper similar to those of G. Staining with PAS for

carbohydrate revealed a strong reaction in the paper strips for G, but only a barely detectable reaction for Su. Hexosamine (Hex-Am) analysis also showed G to be richer in this moiety than Su. The leading anode peak (LAP) contained 30 to 50 per cent of the protein, but almost no Hex-Am. Pepsin determination on fractions corresponding to the various protein peaks showed the enzyme to be associated only with LAP, though not in parallel fashion. The electrophoretic mobility of canine serum albumin (CSA) was similar to that of LAP in several buffer systems, and they precipitated at the same concentrations of $(\text{NH}_4)_2\text{SO}_4$ in salting-out experiments. Experiments with CSA labeled with ^{131}I are currently underway to confirm the probable presence of serum albumin in the LAP fraction. Post-prandial acid juice (PP) exhibited prominent cathodal components, in contrast to the pattern for ACh Mu with its numerous anodal components. This difference may be explained by the finding that *in vitro* peptic digestion of ACh Mu yielded a pattern similar to that of PP.

Histochemical Distribution of Phosphatases in the Liver. Tibor Barka, M.D. (Department of Pathology.) Presented November 9, 1959.

The specific phosphatases of rat liver were studied by histochemical methods in normal animals and under experimental conditions. The latter included acute and chronic ethionine intoxication, ligation of a branch of the portal vein and of the common bile duct, injections with vital dyes and treatment with methylene blue, dinitrophenol and safranin. The applications of different activators and inhibitors suggest that in the rat liver (a) there are four different ATP-ases, localized in the wall of bile canaliculi, in the Kupffer cells, in the cytoplasm (in mitochondria), and in the wall of large vessels; (b) there are at least two different 5-nucleotidases, localized in the bile canaliculi and in the peribiliary granules and in the wall of sinusoids and in the Kupffer cells; (c) there is no histochemical indication of different types of acid phosphatases and there is not enough evidence to assume the presence of a specific phosphatase active at pH 7.2 in the peribiliary granules and in the Kupffer cells. Experiments are underway to verify the presence of these enzymes by separation on acrylamide gel. Some of the changes observed in different conditions seem to be nonspecific and expressions of cell damage. The changes of the activity and distribution of acid phosphatase were particularly studied, using a modified azo-dye method. The formation of large, acid phosphatase containing globules and an increase of acid phosphatase activity following the ligation of the portal vein were observed. The droplets are probably derived from the lysosomes, characterized histochemically by high acid phosphatase activity. These are peribiliary and probably contain PAS positive material as structural components. They probably play a role in pigment deposition and bile secretion.

Further Observations Supporting the Enzyme Deficit Theory of the Cause of Essential Hypertension. Milton Mendlowitz M.D., H. Weinreb, M.D., Nosrat Naftchi M.S., and Stanley E. Gitlow, M.D. (Department of Medicine.) Presented December 4, 1959.

Reactivity to l-norepinephrine (NE) was determined in the digital circulation of 20 normotensive subjects and 20 patients with essential hypertension. The

work of vasoconstriction per mg of intravenously infused NE was measured both before and after the administration of prednisone or prednisolone. After one week of therapy, prednisone produced increase in NE reactivity in some but not all normotensive subjects, but in none of the hypertensive subjects, and after a single intravenous injection of prednisolone (100 mg), NE reactivity was moderately increased in the normotensive but not in the hypertensive group. After three weeks of prednisone therapy (30 mg daily), however, reactivity to NE was doubled or trebled in most subjects of the normotensive group but remained substantially unchanged in the hypertensive group.

These observations support the theory that prednisone or prednisolone inhibits the enzyme which inactivates NE and that there is a deficit of this enzyme in essential hypertension. That the effect cannot be attributed to structural vascular changes is indicated by observations in 20 cases of Raynaud's disease both of the obstructive and vasospastic types where such structural changes as intimal hyperplasia and smooth muscle hypertrophy are known to occur in the digital arteries. NE reactivity was normal in both types of Raynaud's disease. Whether or not a hereditary deficit of the specific enzyme, O-methyl transferase, is the cause of essential hypertension can be established only by appropriate chemical studies.

The Effect of the newer Potent Anticholinergics on the Unstimulated and Secretin Stimulated Pancreatic Secretion in Patients with and without Pancreatic Disease. Therapeutic and Theoretic Implications. David A. Dreiling M.D., and Henry D. Janowitz M.D. From the Pancreatic Research Laboratory, and the Department of Surgery.) Presented November 9, 1959.

An important facet in the medical management of acute pancreatitis is the "splinting of the injured pancreas" by suppression of pancreatic secretion. Although previous investigators have demonstrated that atropine, banthin, and probanthine suppress enzyme secretion about 50 per cent and inhibit to a much lesser extent the volume and bicarbonate secretion of the pancreas, effective utilization of these agents is limited by the cardiovascular and autonomic ganglion blocking side reactions which are undesirable in patients with shock. The present study is an investigation of the action of a series of new potent anticholinergic drugs upon the pancreatic secretion of patients with and without pancreatic disease. All patients were studied by the double secretin test technique.

The results of the investigation indicate that these newer anticholinergic compounds are capable, at doses below those at which undesirable side reactions occur, of inhibiting the unstimulated and secretin stimulated rates of flow, the rate of alkali production, and the rate of enzyme elaboration. The inhibitions observed were in the range of 95 per cent.

It has been concluded that these drugs may be of therapeutic value in the treatment of acute pancreatitis. Some specificity of anticholinergic activity has been observed. Analysis of the data would indicate a greater interdependence of hormonal and nervous mechanisms of secretion. Further evidence has been presented suggesting bicarbonate equilibration in the pancreatic intralobular ductules.

In Memoriam

DAVID ADLERSBERG

1897-1960

David Adlersberg came to New York in 1931 at the age of thirty-four. He had already gained widespread scientific recognition. Born in the northeastern provinces of the Austrian empire, he had gone to Gymnasium in Vienna and had obtained his doctorate degree in medicine at Vienna University in 1921. Attracted from the beginning of his scientific career by problems in physiological chemistry, he worked under v. Noorden on water metabolism, on the relationship of hyperventilation to tetany and on the significance of ammonia in the blood. With Porges he studied the use of low fat diets in the treatment of diabetes.

At the time when the concept of the steroids was just developing and when this term comprised only the bile acids and cholesterol, he studied the clinical and pathological effects of natural bile acids and especially of their derivatives. Important studies on the choleretic and cholagogue action of bile acids led to the introduction of Decholin,[®] the sodium salt of dehydrocholic acid as an important and eminently practical choleretic.

Numerous American physicians had been his pupils in the postgraduate courses which he gave at Vienna University and they remained his life long friends. The Mount Sinai Hospital in 1931 had the foresight to offer him the opportunity to pursue his important laboratory studies; these facilities gradually expanded and led in 1952 to the establishment of the present Nutrition Laboratory. As a member of the Department of Chemistry, he first engaged in a study of vitamin A and carotene and later in the study of cholesterol. Among the vitamin A problems, the vitamin A tolerance test should be mentioned, which in Adlersberg's hands gained great importance for the study of tropical and non-tropical sprue, and the malabsorption syndrome in general. The absorption of vitamin A was found to be influenced by the various lipids in the diet. When the cortical hormones appeared in clinical medicine, he introduced cortisone in the treatment of sprue.

Amongst other subjects David Adlersberg was interested in gout. This led to the investigation of the fluctuations of bound and unbound uric acid in this disease and under the influence of various drugs.

Adlersberg was in the vanguard among those who recognized the importance of cholesterol metabolism not only for arterial disease, but also in idiopathic hyperlipemia and hypercholesteremia. He investigated the correlation of these conditions with the different forms of xanthomatosis. With the help of statistical analysis he disentangled the hereditary relationship between hypercholesteremia and xanthomatosis on the one hand and the familial tendency for arterosclerosis and coronary disease on the other hand. Two years ago he spent a few weeks in the Jewish Ghetto in Rome to study the relationship between the nutritional and the racial factors in hypercholesteremia. Similar studies of various racial



DAVID ADLERSBERG

1897-1960

groups in the United States and also of the Hutterites, a religious sect of vegans, followed.

Besides these major projects which Adlersberg pursued with vigour and consistency, he published numerous individual studies on a great variety of conditions which he met on the wards and in his private practice. They show a rarely attained combination of clinical, physiological, and morphological knowledge and insight.

While David Adlersberg must have been conscious of his severe illness during the last two years, he appeared to ignore it with fortitude and, with his usual energy, he kept up both his medical practice and his research work in the laboratory and in the clinic. With all these voluntary duties, he found time to treat all laboratory personnel free of charge.

Not only his family are mourning him but also his devoted collaborators, his patients, his colleagues and his friends. While his life's work was cut off so abruptly at too early an age, we may take comfort from the fact that he has led a full and happy life with all its rewards. We shall best honor his memory by emulating him as a wonderful person and a true physician who was capable of combining medical practice and medical research in the best tradition of two continents.

HARRY SOBOTKA, Ph.D.
for the
Editorial Board

STUDIES IN EXTERNAL PANCREATIC SECRETION. SURGICAL AND EXPERIMENTAL PROCEDURES USED IN THESE INVESTIGATIONS*

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Experimental study of the physiology of pancreatic secretion has always been complicated by the difficulty of collecting its secretion quantitatively and without contamination. Studies on human pancreatic juice are based on collections by duodenal drainage. Such collections are often contaminated by bile, intestinal, or even gastric secretion, and are therefore quantitatively unreliable. Experimental methods for the quantitative collection of uncontaminated pancreatic juice from dogs have been devised or modified by various investigators, but the only one which has proven generally satisfactory is that reported by Thomas and Crider (1). Because of the technical difficulties in preparing and maintaining such animals, and our general success in this regard in recent years, it seems worthwhile to report some of the details of our technique, for the benefit of other workers who desire to enter this field of investigation, especially since the original paper (1) is rather meager in these respects.

It is desirable to use female animals because they are generally easier to handle during experiments; also, they present less risk of contamination of dressings by urine. As large an animal as can be managed conveniently should be selected since the structures are then more easily identified. An upper midline incision of convenient length for adequate exposure minimizes bleeding and lends itself to easy closure. The duodenum, being mobile, can be delivered through the incision easily. Following this, the lesser pancreatic duct is ligated, so that all external secretion will be delivered through the major duct alone. Since the accessory duct enters the intestine at right angles to the terminal portion of the common duct, it can be identified in this location as a thin white strand (less than one mm in diameter for dogs of average weight) which joins the firm biliary cord as the latter passes through the duodenal wall. Several small vessels between duodenum and pancreas in this region must be ligated and divided (taking care to avoid damage to the gland or to the pancreatic duct itself). Following this, the duct is dissected free for 3 to 4 mm and is then sectioned between two ligatures.

Up to this stage, the dissection is best performed on the posterior aspect of the duodenum, with the pancreas and bowel rotated medially. Now attention is directed to the anterior aspect of the duodenum. The point of insertion of the

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* This work was supported in part by a grant from the Altman Foundation.

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major pancreatic duct can be identified using the following landmarks: (a.) It is just proximal to the point at which the pancreas swings from its close proximity to the duodenum into the duodenal mesentery, approximately 2 cm below the common and accessory pancreatic ducts. (b.) There is usually a little tuft of blood vessels in fat and peritoneum overlying the duct and encroaching on the duodenum, and these vessels must be divided between ligatures in order to expose the duct. (c.) The pancreatic duct can usually be palpated in the groove between duodenum and pancreas at the site described. Final location of the duct is facilitated by transillumination.

After dissecting the major pancreatic duct for several millimeters, for clear visualization, a site is selected for duodenostomy. Since the major duct is somewhere anterior to the sagittal plane, the duodenal incision must be made slightly posterior to this plane, so that it is diametrically opposite the duct opening. An initial incision (1.5 cm in length) is made longitudinally, and this is enlarged upward or downward (to a total length of 3 cm) in such a way that the terminal end of the pancreatic duct will be opposite the center of the incision and just distal to it. The elliptically phlanged portion (A, Fig. 1) of the Thomas cannula (2) is inserted into the duodenum and aligned so that its short vertical extension (B) protrudes through the duodenotomy. The position of the duct in this opening must be verified. The cylindrical portion of the cannula (C) is then screwed on to B, and tightened by hand with the bowel grasped with a moist sponge. The use of internal wrenches as devised by Thomas has not been found necessary. At this stage, the duodenotomy must be closed snugly around the cannula. This is done with a purse-string suture of #00 silk, placed through serosa and muscularis only, so that the mucosa will be inverted when the purse-string is tied. One such tie usually makes the cannula water-tight. After tying, the position of the duct outlet within the lumen, relative to the cannula, is again checked visually. The omentum is now brought over the cannula and a small rent made in it through which the cannula is passed. This leaves a collar of omentum lying on the duodenum around the projecting cannula, to act as a safeguard against leakage. The exterior metal tube (D) is now screwed down on the hard rubber cylinder as far as possible without compressing the underlying soft tissue, and the device is ready to be exteriorized through the abdominal wall.

There are two major considerations in regard to the position of the abdominal incision for the cannula. (a.) It should start cephalad as far as possible, in order to produce minimal downward traction on the duodenum. The best site is usually just below the costal margin, rather than right at the rib; otherwise, the cannula may cause some pressure on the rib. (b.) It should extend posteriorly as far as possible; since the duodenotomy has been placed on the posterior aspect of the gut wall, this location will minimize torsion of the duodenum. Furthermore, this site gives maximum accessibility to the cannula when the dog is standing for collection of secretion. An incision about four cm long is made through all layers of the abdominal wall, at the chosen site. The phlange (E) on the metal tube is grasped with a heavy clamp placed through the incision, and so drawn out to the exterior. Final adjustments are made in the omental

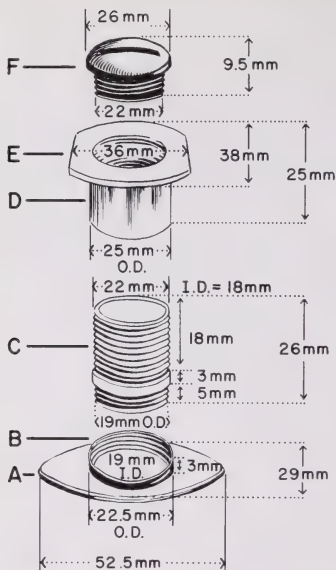


FIG. 1. Diagram of Thomas' duodenostomy cannula separated into its several parts. A. Intraluminal phlange—elliptical (hard rubber). B. Circular collar extending from A; inside thread. C. Male part of cannula; detachable extension of B with outside thread (hard rubber). D. Female part of cannula with inside thread (stainless steel). E. Exterior phlange on D. F. Screw-button to close D (hard rubber).

wrapping, the position of the duodenum is checked for regularity of contour, and the location of the duet opening is again checked through the open exteriorized cannula. Following this, the abdominal wall opening around the cannula is closed with single deep sutures on each side.

The midline incision is closed in the usual manner, after several hundred cubic centimeters of sterile 5 per cent glucose in saline have been given intraperitoneally. Our preference is figure-of-eight silk sutures in the linea alba, and a running lock stitch of silk in the skin. The open cannula is plugged with a fitted cork and closed with a screw button (F), which is always kept well lubricated with mineral oil to permit its easy removal. At no time has this cannula interfered with bowel continuity, nor failed to prevent loss of intestinal secretions. It is not necessary to place any dressings on the operative wound. However, dogs tend to bite at the exteriorized cannula; to prevent this, a heavy canvas coat is laced around the body, and changed as often as necessary.

Post-operatively, the animals are given Combiotic (P.S.[®]) daily for three days. They are allowed to drink water *ad lib* starting 24 hours following operation. Feeding is started on the second post-operative day. During the first week, the daily ration comprises a mush of 150 Gm of Kibbled Meal (previously soaked in

water to soften), 100 Gm of ground horse meat (Pard), and 200 ml of milk. Starting with the second week, this is changed to a stock diet of 300 to 400 Gm of Kibbled Meal and 200 to 300 Gm of Pard per day. Thereafter, the oral intake of this mixture is increased progressively, if necessary. About three weeks post-operatively the animals are ready for training for experimental work.

Following our initial experience with this surgical procedure, there have been no post-operative losses. Subsequent survival time of these animals varies considerably, up to as long as five years, during which they have been used intermittently. Occasionally, a fistulous tract has developed between the lumen of the duodenum and the skin adjacent to the cannula. In most cases, these leaks have stopped spontaneously, or else they have been so slight as to cause no complications in experimentation. With several dogs, the leakage has been so great as to require sacrifice of the animal. It sometimes happened that, in the course of time, the duct opening would migrate cephalad, relative to the cannula. When this occurred, catheterization grew progressively more difficult, and ultimately impossible, so that use of the animal had to be abandoned. This difficulty

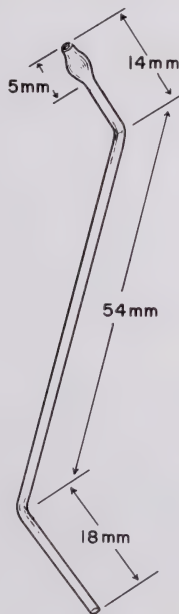


FIG. 2. Diagram of glass cannula for pancreatic duct. Tubing: O.D. 1.5 mm; I.D. 0.6 mm. Bulb: O.D. 2.5-3.0 mm. Angles: Variable, about 135° .

arose only in our early experience, and it has apparently been overcome by placing the duct opening 1 to 2 mm distal to the center of the cannular aperture, as described above.

In general, it has always been our policy to use each dog not more often than twice a week. For each experiment, the dog is placed standing on a canvas sling, after having been fasted for 18 to 24 hours so that the duodenum will be found empty. In the early pancreatic work in this laboratory, the sling was supported in a movable stand of the kind usually employed for collecting gastric specimens from pouch and fistula dogs. In recent work, however, this stand has been replaced by a series of holes in the edge of an overhanging metal shelf, firmly attached to the wall. The screw cap and the underlying cork are removed from the cannula, the intestinal debris is gently mopped out with gauze, and the papilla which marks the entrance of the pancreatic duct is located with the aid of a spotlight. The duct can be cannulated under direct vision with a bent glass capillary tube of the kind described by Thomas and Crider (Fig. 2). It has been our experience that the angle of the inside bend must be varied, according to the individual animal, but it is generally in the neighborhood of 135° . The bulb at the tip is essential, not only to minimize the likelihood of its slipping out of the duct, but also to prevent loss of pancreatic juice around the outside of the glass tube into the duodenal lumen. The length of the intermediate portion of the capillary, between its two bent ends, is such that the outside arm curves down over the metal phlange on the skin. This glass tube is kept in position by wedging a slotted piece of sponge rubber around it and within the cannula. As collecting device, we attach a length of polyethylene tubing (I.D. ca 2 mm., O.D. ca 2.5 mm.—animal tested) to this glass tube, and lead it into a suitably supported centrifuge tube. In this manner, pure pancreatic juice can be collected quantitatively and without any contamination whatever.

The chemical procedures in these studies are those usually employed in such work, including the Van Slyke manometric apparatus for the determination of bicarbonate as CO_2 , a modification (3) of the Van Slyke method for chlorides* and a flame photometer (Process and Instruments Company) for sodium and potassium.

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* At the present time, the Cotlove chloridometer is being used in this laboratory for the determination of chlorides in pancreatic secretion, and has been found by Drs. Parker and Werther to give data generally in agreement with those obtained by our older method. However, for occasional specimens with high protein content, the two procedures yield slightly discordant values. This discordance and related observations will be discussed elsewhere.

PSYCHIATRIC CONSULTATION IN A GENERAL HOSPITAL

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I would like this paper to stand as a tribute to Clarence P. Oberndorf, affectionately known to all his friends and colleagues as "Obie," who was in a real sense my first teacher in psychiatry and to whom I owe a great debt, not alone for what he taught me but for what he represented as a man and teacher. I hope the paper itself will illuminate, if only tangentially, the dimensions of the man and his contribution to psychiatry, especially as practiced in a general hospital.

I should like to discuss the subject of psychiatric consultation in a general hospital by setting forth my own personal experiences in a variety of hospitals over a period of some thirty years and to draw some conclusions from these experiences, with special emphasis on the changes which have occurred during this time.

It will be understood and, I hope, accepted that my comments about hospitals and people I have known are not so much critical as historical, since the conditions which prevailed in one were pretty much duplicated in all; we all rather grew up together, learning through trial and error and from the increasing body of knowledge about the interrelationships between personality, the emotions and disease. What is at present called psychosomatic medicine was in its beginnings and actually reached its current, quite sophisticated development during the years of which I speak.

When I began my internship at the Beth Israel Hospital in New York in 1924 there was no psychiatrist attached to the hospital; instead there were several neuropsychiatrists whose training, skills, interests and knowledge were all largely concerned with neurology. Except for the most manifest psychoses, which usually occurred following surgery and in the course of infectious illnesses then commonly accompanied by prolonged high fever, psychiatry was entirely ignored, if not unknown. A principal neuropsychiatrist at the hospital was a staunch devotee of the "malingering" illusion; every patient suffering from an emotional disease was marked "suspect" in his book unless rescued by the discovery of organic changes; and the therapy was punitive, judgmental, harsh and, need I add, almost invariably unsuccessful. One goal, however, was routinely achieved: the patient would leave the hospital as quickly as possible and we would be rid of another neurotic who had been occupying precious space needed for those who were "really" sick.

Such a goal was easily accomplished by a variety of techniques: unwillingness or inability to understand, insinuation of guilt and blame and, even more devastating, accusations of willful misbehavior. Overt hostility expressed either in smirking, condescending remarks or harsh physical procedures, and where possible, utter neglect, practically always achieved the objective; and, what is

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more, often led to a denial of symptoms through repression, enabling the "psychiatrist" to discharge the patient as "improved!"

To be fair about it, little indeed was known or understood in 1924 about the types of problems which then, as now, were so common on the wards of the hospital. I recall vividly the intelligent, quick, interested and very anxious young man whose diabetes was impossible to control. This was, of course, a very serious problem in those days when the use of insulin was not universal, and the house staff was diligent in its efforts to help him. One day the mystery was solved when he was found hoisting a huge sandwich up to the ward on a rope, said sandwich supplied by his well-meaning but ignorant family. He was promptly discharged as an uncooperative patient; I wonder what would have been the reaction if someone had suggested that we inquire why a young man, fully capable of understanding the consequences of his behavior, still persisted in it. So far as I can recall, not only did no one know; no one asked and hence no answers were required.

Perhaps even more striking examples of this lack were to be found in the clinic for peripheral vascular diseases. As was to have been expected with a hospital population largely made up of Eastern European, cigarette-smoking Jews, there was a high incidence of thromboangitis obliterans. Whatever the lacks in our knowledge of the patho-physiology of this disease may have been, we knew even then that it was absolutely necessary for these patients to stop smoking. For many of them, however, no threat sufficed—no pleading, no demonstration of the catastrophic amputations certainly awaiting them if they failed to stop smoking. It was not until a good many years later that it occurred to the doctors that there must be a profound, if obscure reason for such self-destructive behavior: an emotional problem requiring skilled psychiatric understanding and management.

Things changed materially and for the better when I got to Mt. Sinai Hospital where I was to work in one or another capacity for twenty years, although it was still a far cry from a psychiatric utopia; not only a long way from the psychiatric service which exists there and in many other general hospitals today, but also far from anything which might even by a charitable definition be called adequate. However, there were the reverberations of a beginning revolution in thinking about many problems and there were a few inspired and dedicated psychiatrists. Their presence made a great and lasting difference.

In 1913 Clarence Oberndorf had organized within the Department of Neurology a psychiatric clinic, of whose existence no official notice was taken until 1924. It had then gained sufficient respectability to achieve quasi-independence even though, at that late date, it still had to hide behind the euphemistic title of "Mental Health Class". This obvious avoidance device was designed to hide the fact that the hospital was harboring within its walls a *psychiatric* clinic. This was, so far as I can learn, the first psychoanalytic clinic attached to a general hospital in this country.

In a paper (1) which makes most interesting and informative reading, called "The Psychiatric Clinic In a General Hospital," published in 1925, Oberndorf

described the clinic at The Mount Sinai Hospital. I must not pause to discuss it at length, fascinating though that would be; I should like only to emphasize a few of his major points. In the first place, he laid great emphasis on the social, community aspects of such a clinic and on the positive values of providing these services outside of the dreaded confines of the mental hospital. He also stressed the importance of the ancillary services, especially occupational therapy, social work and recreation. He recognized the advantages to psychiatry itself of being able to draw on the medical facilities of a general hospital, mentioning in particular certain recent advances in medicine, endocrinology for example, which he felt might shed light on certain psychiatric problems. And, perhaps most important of all, he emphasized the great need to treat the medical and other patients referred to the clinic and to treat them intensively. Thus he writes, "In a few cases of conversion hysteria and compulsion neurosis, a brief psychoanalysis following the technique of Freud and devoting over a half hour three times a week to the patient has been undertaken with satisfactory results."

In those days, Oberndorf's co-workers in this clinic included Lorand, Schonfeld, Silverberg, Broadwin, Spencer Strauss and Monroe Meyer. At times all these people, especially Oberndorf and Lorand, worked on the wards, sharing an unbelievable burden of work with little or no help.

What lay ahead can perhaps best be measured by a brief look at hospital philosophy and the doctor-patient relationships of those days. Although I blush to recall it, I can still remember all too well the vomitus of an hysterical patient collected in a basin and left at his bedside with the admonition that unless he stopped this nonsense, the next time he vomited he would be refed the vomitus, by tube if necessary. Or the heated metal rod that was inserted by rectum if the patient did not "behave." Or the electrode inserted in an enuretic patient's urethra.

If proof is needed of the courage and farsightedness of Obie and his co-workers, you have it in the simple fact that they were never deterred by the incredible hostility and antagonism to psychiatry and psychoanalysis which existed at that time. Herman Selinsky, who began his residency at the same time as I, commented in a recent letter about the Memorial Volume published in honor of Israel Strauss, "It is wonderful to see how much psychiatry has at long last become a legitimate and respected member of the medical family. The youngsters are disbelieving about the sadistic contempt and scorn which were heaped on the heads of the previous generation."

How did this hostility manifest itself? In the first place, despite a seeming interest and acceptance of the value of psychiatric consultation, its use was consistently limited to two types of patients: the utterly hopeless and the utterly trivial. Thus, a patient with ulcerative colitis would be "worked up" over a period of weeks, including repeated proctoscopic examinations, x-rays, etc.; would be treated by medications, diet and sedatives; would be watched while he slowly deteriorated; and then, finally, the psychiatrist would be invited to perform his vaunted magic. I need not emphasize the fact that no psychiatrist did indeed think he had any magical tricks up his sleeve; and certainly not in

so hostile a climate, where one tiptoed gently and sometimes offered an idea or two with the deepest humility.

To be sure, we bragged a bit about our successes and, perhaps prompted by vanity and goaded by the implicit challenge to "show me," sometimes undertook the treatment of patients really beyond help from psychiatry, especially with the minimal time and the few people then available.

The trivial are more difficult to describe but equally distinct as a group. A poor suffering person would say "I wish I were dead," and the psychiatrist would be summoned post-haste to see a "suicidal" patient, often in the middle of the night. The threat should have been recognized as something less than ominous, especially when one recalls that most of these patients were old-world Jews, and that in its yiddish form this was one of the more common laments, not too far removed from the G.I.'s "Oh, my aching back!"

Another patient might make a passing comment to an intern about some minor personal problem not even germane to the illness for which he was hospitalized; promptly an order would be left to call the psychiatrist. Often, when we finally saw him, days later, we were greeted with frank amazement by a patient who had long since forgotten the discussion which presumably occasioned the consultation in the first place.

It should be recognized, of course, that occasionally what looked like hostility was indeed merely the expression of anxiety on the part of the referring person. (Dr. Norman Reider, in commenting on this paper, said, "I saw a consultation today on a woman with a mild post-operative anxiety reaction. I prescribed Miltown: one 100 mg. tablet a day for her and three for her physician.") It is relatively easy to understand such anxiety in the novice or untrained personnel; it is not so plain why such "threats" or even the slightest expression of emotionality should create anxiety in physicians and others, often long experienced in the management of patients. Certainly, it is the psychiatric consultant's job to understand and allay such anxiety in hospital personnel since it so often results in hostility and unsympathetic handling, and ultimately in an increase of the patient's own anxieties. Thus a vicious cycle of mismanagement is set up, obviously deleterious to the best interests of the patient.

Then there were the jokes, cruel and painful. Most of them, as I remember it, were directed at two sore spots: our presumed preoccupation with sex and our failures.

Obviously, the psychiatrist's primary role is the treatment of the sick. Increasingly, he has been able to contribute to treatment in a general hospital through more accurate knowledge of psychodynamics, greater knowledge and skill in the management of emotional crises associated with organic illness and through proper referral for psychotherapy of patients seen in consultation.

In such illnesses as asthma, hypertension, ulcerative colitis, peptic ulcer and hyperthyroidism, the role of the emotional factors has become increasingly clear, if not as yet by any means finally and completely understood.

In the management of such crises as pre-operative panics, post-operative

confusional states, the pernicious vomiting of pregnancy, thyroid storms, etc., the role of the psychiatric consultant is of the first importance.

In most general hospitals the psychiatric consultant has little opportunity to undertake much treatment on the wards of the hospital. The steady demand for consultation, the lack of privacy on the wards and the time required for individual psychotherapy make it almost impossible, except in relatively acute situations. But the consultant has an essential role to play in the screening of patients for referral to the outpatient department for therapy. Since not all patients can or should be treated, this selective process is of major importance, and is more subtle and complicated than might appear at first glance. In this there is no substitute for the clinical sense that grows out of this particular kind of experience.

The request for psychiatric consultation is a rather more complicated situation than is generally true when other specialists are asked to see hospital patients. The indications are often far less clearcut and their significance more complex and obscure.

In the first place, and despite all our efforts at education, people generally dread "psychiatric" help and are apt to react with anxiety, resentment or even flight to the mere suggestion that a psychiatrist be called in consultation. I am sure it is a disappointment to us all to recognize this, but it must be faced. We hear it from our medical colleagues day in and day out and experience it ourselves, especially in contacts with new patients; we still find the most archaic misinformation about psychiatrists and quite primitive attitudes even in people from whom one would not have expected such a response on the strength of their general level of education and intelligence. The fact is that the protest, "I'm not crazy; why do I need a psychiatrist?" is almost reflex, even though it may often be expressed more subtly and indirectly.

I have already mentioned anxiety in the referring person as a possible cause for the misuse of the psychiatric referral. Another common practice is that of calling in the psychiatrist only at the point where the patient has become a problem in management and is making a nuisance of himself to the personnel or the administration ("If you don't behave yourself, I'll call the psychiatrist!"). This is easy to understand, and I would be the last one to make light of the tremendous burdens carried by these who are responsible for the care of hospitalized patients, especially in large groups on wards. But it should be emphasized that the only valid criteria for psychiatric consultation should be the nature of the patient's illness and a reasonable estimate of the potential benefit to the patient of such a consultation.

There are many other facets of psychiatric consultation, some of which warrant at least brief mention. The question of psychiatric notes on patients' charts raises special problems, both as to confidentiality and the possible use of the material in legal actions, especially if it is of a "non-medical" (social, personal) nature. To avoid such difficulties it is now common practice to enter a brief statement noting the psychiatrist's visit, while the actual contents of the inter-

view are recorded elsewhere and remain confidential. This device is at best a makeshift; the basic problem remains unsolved.

The simple statement of a diagnostic impression that usually results from a psychiatric consultation is less than satisfactory. Ideally, there should be an opportunity for discussion of the patient by the referring person, nurse, case-worker and psychiatrist. This would be manifestly unrealistic in most situations, but the fact remains that many psychiatric consultations fail to contribute as much as they might to the patients' well-being and the education of hospital personnel because of this isolation from those who must carry day-to-day responsibility for treatment.

The psychiatrist himself is often handicapped by inadequate information about the patient he is to see: a brief note requesting the consultation but seldom including the reasons for the request. Many consultations lead to the recommendation that the patient be referred for treatment; unfortunately, the psychiatrist seldom learns of the outcome of his prescription. Whether the psychiatrist should assume more responsibility for following up on the patient's progress or the referring person should keep the psychiatrist informed of developments is not the issue. The crucial problem here is a breakdown in communication which can only result in less than optimal service to patients and a generally frustrating and unrewarding experience for the staff.

After all my years of work in general hospitals I believe that the psychiatrist's greatest contribution has been and in a sense still is the growing recognition of the worth of the individual patient, of the dignity and value of the human spirit and the necessity for considering the patient as a feeling person. This may seem naive and unscientific, but it is my conviction.

The dehumanized attitude toward the patient which had become quite prevalent in medicine in the guise of science, and had been catalyzed by enormous strides in pathology, physiology, endocrinology, etc., was relatively new in the 1920's, as new as the budding specialty of psychoanalysis. Much earlier, the physician had this regard for the whole human, the person, which was handed down naturally and inevitably by his priestly forebears. For a long time the general practitioner, the almost legendary family doctor, had occupied an analogous role, only to give way in an age of scientific medicine to specialization and the array of scientific tools. As Zweig (2) pointed out:

"Disease meant now no longer what happens to the whole man but what happens to his organs. . . . And so the natural and original mission of the physician, the approach to disease as a whole changes into the small task of localising the ailment and identifying it and ascribing it to an already specified group of diseases. . . . This unavoidable objectification and technicalization of therapy in the 19th century came to an extreme excess because between the physician and the patient became interpolated a third entirely mechanical thing, the apparatus. The penetrating, creative synthesizing grasp of the born physician became less and less necessary for diagnosis."

And Alan Gregg (2):

"The totality that is a human being has been divided for study into parts and systems; one cannot deery the method but one is not obliged to remain satisfied with its results alone. What brings and keeps our several organs and numerous functions in harmony and federation? And what has medicine to say of the facile separation of 'mind' and 'body?' What makes an individual what the word implies—not divided? The need for more knowledge here is of an exeruciating obviousness. But more than mere need there is a foreshadowing of changes to come. Psychiatry is astir, neurophysiology is crescent, neurosurgery flourishes, and a star still hangs over the cradle of endocrinology. . . . Contributions from other fields are to seek from psychology, cultural anthropology, sociology and philosophy as well as from chemistry and physics and internal medicine to resolve the dichotomy of mind and body left us by Descrates."

It was really the emphasis on the *whole* man that ultimately helped change the attitude of the physician, and especially the psychoanalytic awareness of the *meaningfulness* of all the patient's symptoms no matter how difficult this might be to accept at first glance. We have obviously made real progress toward this goal.

Gradually the psychiatrist appearing on the wards is coaxing the doctor out from behind his white coat and dangling stethoscope to take a look at a man and to talk with him and, most of all perhaps, to be willing to listen and try to understand.

I have told this incident to a generation of students and residents but I hope it will bear still another telling. Patients with hyperthyroidism were treated at The Mount Sinai Hospital in the 1920's by a method devised by Kessel and Hyman (3) which they called, euphemistically, "skillful neglect." Despite their awareness that emotional factors were involved, at least in precipitating the illness, the treatment consisted essentially of bed rest, warm packs, sedation and frequent feedings of food with high caloric value. It also consisted, obviously and importantly, of making the patient feel "special," one of a favored few, the object of special concern on the part of the nurses, house staff and particularly the "chief," the professor, if you will. I need not elaborate the psychological factors involved in the apparent success of such treatment in gratifying every infantile wish, oral, tactile, narcissistic, etc.

One day a patient with hyperthyroidism was admitted to the Neurological Service for reasons that had nothing to do with the patient or her illness. At any rate, she came under the management of the neurologist, and Obie sort of bootlegged me into being her psychiatrist. It was then early in my residency in neurology, and my psychiatric education had been limited indeed.* I had never even taken a psychiatric history. When I begged Obie to tell me what to do, he suggested that I talk to the patient about herself and listen carefully to anything she had to say. This I did and gradually a person unfolded—hopes, illusions, disappointments, crises, conflicts, defenses and all—and with Obie's

* In 1920, the year I entered the College of Physicians and Surgeons, the entire psychiatric instruction consisted of one hour per week of lectures during the winter session of the fourth year.

gentle prodding and some very hard work, I gained my first awareness of an entirely new dimension in the relationship of doctor and patient.

This may seem quite trivial, but it is just this shift in emphasis, in values, in tolerance and understanding, that I think is so fundamental. No longer is the doctor limited to the study of an ill-functioning or diseased organ; no longer need he be exclusively concerned with the mass, the specimen, the chemical calculation, the changes in electrical conductivity. No longer need the main object of study and concern be this "interesting" mass to be palpated or that "wonderful" sound on the inside to be picked up, all subsequently to be discussed within the hearing if not the comprehension of the patient.

One of the first things I learned from Obie and others was respect for the sick person. This went beyond sympathy and patience and beyond devoted attention to the illness, all of which were deeply imbedded in the philosophy of the hospital. Respect included a different dimension of understanding the worth of the person and the meaning to him of his sickness and all the experiences associated with his treatment.

Talking to a group of general practitioners ten years ago, Rennie recalled that when he was an intern they went on "grand rounds" and wheeled about large cases of autopsy material—kidneys, lungs, or some other pathological substances illustrating what the patient was presumably suffering from (4):

"We wheeled these out before the patient, and we discussed in front of him all the details of his condition in a conversation which might go somewhat like one I heard a week ago in a large hospital in New York City. A seventeen-year-old boy lay in his bed, and about twenty doctors were grouped around him. They discussed the pros and cons of what the pathology in his abdomen might be. One doctor said, 'I think he has a hypernephroma.' Another offered his tentative diagnosis, and a third said, 'Why he's exactly like that patient we had on the third floor a couple of months ago.' Someone asked, 'What happened to him?' 'Oh, he died. He died last week.' A fifth doctor said, 'Have we any slides of this thing?' Whereupon another doctor said, 'Of course we haven't any slides; the patient is still living.' Then the doctor who had asked about the slides said, 'Well, we'll probably get them in a couple of months from now.' And the seventeen-year-old patient lay in bed listening to this conversation."

This attitude toward the patients, especially as seen on rounds, was one of the most disturbing things to me. Not only did it seem that no thought was given to how such rounds might be used positively in the management of the patients; they were often highly destructive and paradoxically, the perpetrators were essentially kind and devoted men.

It is my impression that the presence of the psychiatrist and his active participation, both as consultant and member of the team on a given service, medical or surgical, have made for considerable improvement in the management of rounds, especially in the avoidance of the shocking and demoralizing bedside discussions of the patient. However, a recently published and highly illuminating study by Kaufman, Franzblau and Kairys (5) at The Mount Sinai Hospital suggests that the wish may be, at least in part, responsible for this impression.

Although the study had a much wider scope than this particular aspect of hospital care, some of the reported incidents, such as the discussion of a patient's terminal illness in her presence, indeed seem to turn back the clock.

The psychiatrist can do much to implement this study's emphasis on "the need for respect for the patient's person and privacy," which is indeed a major premise of psychiatry itself. The psychiatrist knows and can teach his colleagues such things as the meaning of the authoritarian role played by the "big doctor, the chief"; can demonstrate that even the patient who seems most withdrawn and too sick to understand, does hear and must ruminate on the meaning of the half-understood and barely perceived comment; and can try to make clear to his colleagues the influence of all such emotional stresses on a patient's illness and recovery.

One of the inevitable by-products of this new interest in the patient as a person is the increased readiness of the hospital staff to observe and respond to deviations in the patient's behavior. This is true for doctors—especially the interns and residents—nurses, social workers, and occupational therapists, among others. Although he is generally asked to see a patient, as consultant, by the physician in charge, it is not at all rare these days for a nurse who has observed some bizarre piece of behavior in a patient or been made party to some anxiety-producing confidence to ask through the appropriate channels that a psychiatrist be called in consultation.

More importantly, a growing bond of useful and skilled collaboration has developed between the social service and psychiatric departments as they have, in a sense, grown up together. Although this is not the place to discuss it, the interaction between the social emphasis of case work and the dynamic (psycho-analytic) insights of psychiatry has many fascinating and significant ramifications. Suffice it to say here that each has contributed to the other, formally and informally. Today social work has its own highly developed therapeutic armamentarium in which, when indicated, it may judiciously use psychiatric consultation. Similarly, psychiatry has learned to make effective use of the skills of case work in what has become, in and out of the traditional clinical team approach, a most fruitful and happy collaboration.

The psychiatrist teaches as he goes, literally as well as figuratively. Of all the teaching tools I know, none is more effective than discussion by the psychiatric consultant of a patient or group of patients on the ward or in a clinic with those directly responsible for the actual care of patients. I have never ceased to delight in the interchange among nurse, social worker, resident and psychiatrist in the informal atmosphere of the day room, and its educational potential. Of course, I do not mean to imply that the tremendous advances in these professions have resulted from such informal infiltration of psychiatric ideas alone, but they have helped, I think, more than is generally recognized.

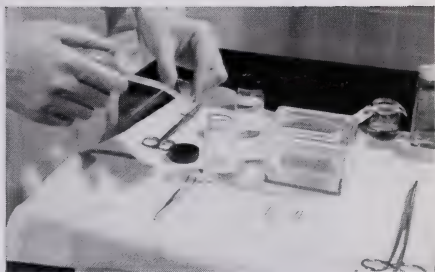
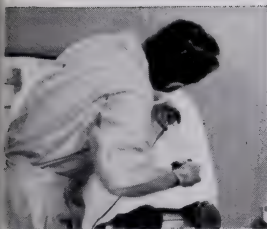
One of the chief beneficiaries of the educational role inherent in psychiatric consultation in a general hospital has been the psychiatrist himself. When the psychiatrist emerged from the psychiatric hospital where his work had been restricted to the care of the mentally ill, and began to work actively with this

group of general medical and surgical patients, he added a whole new dimension to his work and an opportunity for a type of experience he had previously been denied. This taught him a very different approach to illness and afforded new and startling illustrations of his developing psychodynamic formulations. Out of this, indeed, grew a whole new branch of psychiatric practice, psychosomatic medicine. Indeed, as we are only now beginning to realize, we went too far in this quasi-specialization and corrective insights are already being applied.

Most of all, psychiatry can give the doctor the tools to understand the person and to learn the meaning of the symptoms and the illness. No doctor thus armed can ever again neglect the patient in his human aspects or slight the dignity of his human needs and wants. "In their simplest form the ingredients of dynamic understanding and relationship can be reduced to the words respect and affection. If you like an individual for himself, you can disapprove of something he does while continuing to like *him*; if you respect him as a human being, you assume his right to think and feel as he does and to be the kind of person he is" (6). Assuming this, the doctor who wishes to treat a patient must try to understand how and why he thinks and feels as he does, insofar as his feelings affect and are in turn affected by the illness which brings him to the doctor. I would only like to repeat that I believe this may in the end prove to have been the psychiatrist's greatest contribution to medical care in the general hospital.

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GASTRIC ULCER DEVELOPING AFTER ESOPHAGECTOMY FOR CARCINOMA

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New York, N. Y.

The problem of a gastric ulcer developing in the residual stomach of patients who have undergone esophagectomy or esophagogastrrectomy for carcinoma of the esophagus or cardia, respectively, may be a difficult one to resolve. The difficulty becomes compounded if the interval between the detection of the ulcer and the previous surgery is a number of years. Previous publications have suggested benign gastric ulcer as a common cause of the roentgenographic deformity in these cases. Nevertheless, such benignancy is not always the case.

The purpose of the present paper is to emphasize another mechanism involved in the development of gastric ulcers in such patients.

CASE REPORTS

Case 1

(P. M., #105724). This was the first admission to The Mount Sinai Hospital of this 62 year old white male who presented himself with melena of five days duration in December of 1958.

In December 1955, the patient had an esophagogastrrectomy performed at another hospital for adenocarcinoma of the cardia and lower end of the esophagus with no involved lymph nodes in the resected specimen. Pyloroplasty or gastroenterostomy was not done. The patient was periodically followed with barium series at the other institution. The last study had been done in January 1958, and was reported as showing no changes from the previous postoperative examination, with no evidence of recurrent disease.

Since surgery, the patient had intermittent mild left upper quadrant and lower left chest pain. In the previous five or six months there had been ribbon-like stools, with increasing constipation. Five days prior to admission, for the first time, the patient noted the onset of melena. The remainder of the history was non-contributory, although it was noted that the patient's mother died at the age of 52 of carcinoma of the stomach.

Physical examination revealed no significant abnormalities. There was a left thoraco-abdominal incision, well healed, with the posterior part of the left eighth rib absent. Breath sounds were diminished over the left base posteriorly. The heart was normal. Abdominal and rectal examination were negative as was the remainder of the physical examination.

Laboratory data included hemoglobin of 11.1 grams per cent, hematocrit of 38 per cent and white count of 7600 cells per cubic millimeter with a normal differential except for 10 per cent eosinophils. Guaiac studies of the stool were 4 plus on two occasions and 2 plus on one occasion. Gastric analysis revealed 10 units of total acid and no free acid in a fasting specimen. Fifteen minutes after histamine, the acidity rose to 90 units total and 75 units free. Barium enema was negative.

A barium examination of the stomach and duodenum was reported as showing no delay at the esophagogastric anastomosis. The intrathoracic portion of the stomach showed retained secretions and a coarse mucosa, but appeared to be distensible. In the mid portion of the stomach, at the level of the diaphragmatic hiatus, there was a smooth, well defined ulceration projecting outside the expected contour of the stomach and measuring about 1½ centimeters in diameter on the lesser curvature portion of the stomach. The stomach in

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FIG. 1. Barium meal shows no delay to the passage of barium into the thoracic portion of the stomach which is distended with air and secretions. Barium passed freely through the hiatus, but the stomach is narrowed at this level and a discrete smooth ulcer crater is evident (arrow). This has the appearance of a benign ulcer. The remainder of the stomach does not appear remarkable.

this region was markedly narrowed, presumably because of diaphragmatic constriction. This narrowed area did not change in size and there was no evidence of any rigidity in this region (Figure 1). The infradiaphragmatic portion of the stomach appeared to be normal. The radiological impression was that of a benign ulcer. Chest film was noncontributory and fluoroscopy revealed no motion of the left hemidiaphragm.

Esophagoscopy revealed that the anastomosis was at 29½ centimeters from the incisors, was patent and that the mucosa in this area was smooth. The stomach showed full rugae. No ulcerations or masses were seen to a distance of 45 centimeters from the incisors. Biopsy of the fullest ruga was reported as normal gastric mucosa. Sigmoidoscopy also was performed and was negative to ten inches from the anal verge.

On January 2, 1959, an exploratory thoraco-abdominal laparotomy was performed. At operation, there was extensive infiltration of the stomach wall in circular fashion, by tumor, all along the lesser curvature. The stomach was fixed posteriorly with tumor extending posteriorly, invading the diaphragm and retroperitoneal structures and causing a marked narrowing at the level of the diaphragmatic insertion. Peritoneal implants were found. Biopsy of the gastric wall was reported as showing a segment of smooth muscle infiltrated with undifferentiated carcinoma, with some signet ring cells. Biopsy of the diaphragm showed a few foci of metastatic undifferentiated carcinoma.

Postoperatively, the course was uneventful and the patient was discharged to be followed in the Out Patient Clinic.

Case 2

(G. B., #59947). This 68 year old white female was admitted for the second time to The Mount Sinai Hospital in February 1959, because of weakness, dyspnea and pallor of several weeks duration.

Her first admission to this Hospital was in January of 1956, with a six months' history of dysphagia and weight loss.

A squamous cell carcinoma of the esophagus was found 22 centimeters from the incisors and on February 7, 1956, the patient underwent esophagectomy with supra-aortic esophagogastrostomy, with no drainage procedure. There were no involved lymph nodes. The post-operative course was uneventful.

The patient was clinically well until October of 1958, 32 months after operation, when she



FIG. 2. Barium meal examination shows the dilated supradiaphragmatic portion of the stomach, which contains considerable secretions or retained food. Barium, however, promptly entered the infradiaphragmatic part of the stomach through the hiatus of the diaphragm. On the posterior wall of the stomach (arrow) there is a hemispherical filling defect narrowing the AP diameter of the lumen of the stomach. Within the defect, there is a huge irregular ulceration. The distal part of the stomach does not appear to be involved and barium left the stomach promptly.

developed hoarseness. Indirect laryngoscopy revealed abductor paralysis of the right vocal cord. The patient received radiotherapy to the mediastinum with only slight improvement in the hoarseness. In January of 1959, a hemoglobin of 9 grams per cent was noted. This was treated with oral iron. In the three weeks prior to her present admission, increasing pallor, weakness, dyspnea and a ten pound weight loss were noticed by the patient. The remainder of the history was noncontributory.

On physical examination pallor was found, and a grade 3 systolic murmur at the base and apex, transmitted widely. The liver edge was felt three finger breadths below the right costal margin and was sharp, firm and non-tender. There were no other unusual abdominal findings. Rectal examination revealed grey stool that gave a 4 plus guaiac reaction.

Hemoglobin was 5 grams per cent, hematocrit 15 per cent and the white count 3250 cells per cubic millimeter with a normal differential. Examination of the bone marrow showed erythroid hyperplasia with eosinophilia. On four occasions, stool guaiacs were 4 plus. Gastric aspiration yielded dark brown fluid that gave a 4 plus guaiac reaction. Free acid was present in the gastric aspirate only one hour after the injection of histamine.

A gastrointestinal series revealed the anastomosis to be intact. In the distal stomach, beginning just about at the level of the diaphragmatic hiatus, there was a large mass, about 6 centimeters in length, on the posterior wall. Within this mass was a large irregular crater. There was considerable narrowing and rigidity of the stomach in the region of the mass. The distal few centimeters of the stomach did not appear to be involved (Figure 2).

On March 2, 1959, an exploratory laparotomy was performed. There were enlarged, firm, perigastric, peripancreatic, celiac and mesenteric nodes. The group of involved celiac nodes was firmly adherent to the posterior wall of the stomach, forming a large mass in this region. Biopsy of an involved node from the transverse mesocolon showed metastatic squamous cell carcinoma.

The postoperative course was uneventful except for the development of a mild right upper lobe pneumonitis that cleared by the time of discharge.

DISCUSSION

In the first case, the radiological impression was that of a benign gastric ulcer developing three years after esophagogastrrectomy for adenocarcinoma of the cardia. This patient had no free acid on a fasting specimen and after histamine stimulation, the free acidity rose to 75 units. Although no insulin test was done, completeness of the vagotomy in this patient is evident because of the previous operative procedure of resection of the distal esophagus and proximal stomach.

It has recently been pointed out that benign gastric ulcer may be a complication of esophagogastric anastomosis with resection of carcinoma of the cardia or of the esophagus (1, 2). Smith (1) reported four cases; one had low free acid nocturnally but a negative insulin test; one had free acid only after histamine stimulation (no insulin test done); and two had no secretory studies performed. One of the latter patients had only a lateral esophagogastrostomy performed without resection because the operative impression was that of benign stricture, although the autopsy findings showed carcinoma of the cardia. Hence, this patient had no vagotomy. In these cases the interval of time between operation and onset of ulcer symptoms was from one to three years. In two of the cases the patient died of massive gastrointestinal hemorrhage and autopsy showed benign gastric ulcers. In one case, the ulcer was surgically removed and proved to be histologically benign and in the fourth case benignity was assumed since after gastroenterostomy the patients symptoms and x-ray evidence of the ulcer

disappeared. Smith proposed that these ulcers are secondary to gastric retention, although only one of his cases showed definite x-ray evidence of this, and he recommended that gastroenterostomy or pyloroplasty should accompany the original resection.

Other cases of benign peptic ulceration of the stomach after esophagogastrrectomy or after esophagectomy have been reported (3, 4). Dreiling (5), however, studied eight patients who had an esophagogastrrectomy for carcinoma of the cardia or of the lower esophagus and found that only one had persistent gastric acid secretion postoperatively. As he points out, in this age group and in patients having gastric cancers, the incidence of those patients with persistent gastric acid secretion will be low.

In our second case, the lesion was radiologically an obvious ulcerating carcinoma. However, the question of whether such a lesion represents a new primary growth or a metastatic lesion is a very real one. That carcinomas of the esophagus (6-8) or gastric cardia (9, 10) can metastasize to the distal stomach has been known for many years. For esophageal lesions, Palmer (11) states 15 per cent of autopsied cases showed invasion of the stomach. It has been shown, also, that in cases of primary carcinoma of the esophagus, apparently discrete ulceration of the stomach is due usually to outcrops from metastatically permeated submucous or subserous lymphatics (12-16) and similar metastatic ulcerations may occur in cases of primary carcinoma of the stomach (17). Borrmann (15) has also shown that secondary invasion of the stomach from metastases to surrounding lymph nodes may simulate the appearance of an independent primary gastric lesion.

Our first case may represent mucosal ulceration of metastatic subserous or submucous tumor, or may represent secondary invasion from surrounding metastatic lymph nodes. The second case undoubtedly represents the latter.

SUMMARY

Two cases are reported of gastric ulcer occurring three years after esophagogastrrectomy and esophagectomy, with esophagogastric anastomoses, for carcinoma of the gastric cardia and the middle third of the esophagus, respectively. In the first case, the lesion appeared radiologically benign; in the second case, the lesion appeared malignant on x-ray. At surgical exploration both cases were found to have ulcerating metastatic lesions.

The question of benign gastric ulcer following esophagogastrrectomy or esophagectomy is discussed. It is emphasized that the gastric ulcer may arise from surrounding, infiltrating metastatic lymph nodes or from ulcerating submucous or subserous lymphatic spread of the primary tumor.

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THE ESOPHAGOGASTRIC CLOSING MECHANISM

ROLE OF THE ABDOMINAL ESOPHAGUS

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In a previous report (1), the roentgen features of the gastroesophageal segment or vestibule and the sphincteric nature of this region were described. Intraluminal esophageal pressure studies (2-6) also demonstrate the existence of a high pressure zone in the terminal 2 or 3 cm of the esophagus to which the term gastroesophageal sphincter has been applied. These studies indicate, however, that this area is not a very potent sphincter. The pressure that it can resist varies from about 6 to 16 cm of water. In contrast, in normal individuals, the intra-abdominal pressure can be increased to 100 cm of water before reflux of gastric contents into the esophagus will occur (7, 8). It is therefore clear that the closing mechanism in the esophagogastric region must include other more powerful factors.

The suggestion that a discrete mucosal valve exists at the cardia has received little support. In a detailed investigation of the rugal pattern at the cardia, Botha (9) has demonstrated that the rugae in the region of the cardia normally are in close apposition and form a star-shaped or crescentic configuration. It is not the claim of this author that these rugae overlap each other in such a fashion as to create a valve but rather that they form an interdigitating arrangement which can serve to make closure complete and watertight. These interdigitating folds at the cardia have been referred to as the gastric rosette. In the human, however, there is no evidence that this rosette actually protrudes any considerable distance into the lumen of the stomach at any phase of deglutition. The term rosette is more applicable to the appearance seen on esophagoscopy when a point 2 or 3 cm from the esophagogastric mucosal junction is reached. At this site, the further entrance of air under atmospheric pressure does not occur because of persistent closure; the redundant mucosal folds protrude into the lumen above. There is no change in the appearance of either the esophageal or gastric rosette with phase of respiration. In its closed state, therefore, the terminal 2 to 3 cm of the esophagus, to the cardia, are filled by apposed mucosal folds and the entire region might be referred to as the rosette canal (Fig. 1). This region corresponds to the sphincteric area of the terminal esophagus and the persistent closure evident on esophagoscopy appears to be evidence of this phenomenon. The distal portion of this canal consists of the abdominal part of the esophagus. In view of the fact that these folds are so closely apposed to each other, it is somewhat surprising that more emphasis has not been placed on the adhesive or cohesive forces between them as part of the mechanism maintaining esophagogastric closure. It is conceivable that the interfacial tension that must be over-

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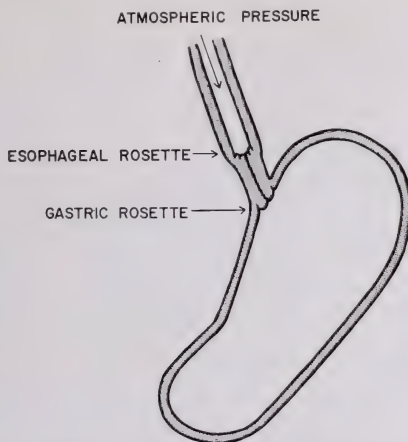


FIG. 1. The "rosette canal". In the resting state, the terminal portion of the esophagus and the cardia are closed by intrinsic sphincteric action of this area. The mucosal folds are closely apposed and squeezed proximally to form the esophageal rosette. The rugae at the cardia form the "gastric rosette". On esophagoscopy, this canal fails to open under the pressure of atmospheric air introduced through the tube but is easily entered by manual pressure on the esophagoscope applied to the center of the rosette. The gastric rosette is difficult to identify from the gastric side and also does not change in appearance with respiration. The rosette canal corresponds to the sphincteric portion of the esophagus; its distal part is the abdominal esophagus.

come before this segment can be opened could be quite large. A film of water, for example, is said to be capable of withstanding a pull of 3,600 mm of mercury per square centimeter (10). A feature of this type of closing mechanism would be an apparent valvular action in the sense that, when the surfaces do separate, the total pressure is abruptly applied intraluminally and the area will distend promptly. In order for this segment to open, from either side, the force must be applied exactly in its center. A funnel-shaped arrangement into the center of the rosette is a physiological feature at the proximal end, that is, during distension of the esophagus. Under normal circumstances, no such funneling entrance to the rosette canal is present on the gastric side. It is worthy of note in this connection that, as the stomach fills, the region of the cardia and adjacent lesser curvature are not stretched to any significant degree. Moreover, there is no remarkable increase in intraluminal gastric pressure until distension becomes excessive. During gastric filling, therefore, the apposition of the rugae in the region of the cardia is not greatly disturbed.

It is likely that, if the mucosal folds in the rosette canal were covered with a simple film of water, the interfacial tension would be excessive for the physiological responses required. The mucous secretions of the cardiac glands in this

region are presumably adapted to produce a more suitable surface film. It is likely therefore that the interfacial tension which must be overcome during opening of this segment is quantitatively not much greater than the intraluminal pressure created during closure by intrinsic sphincteric contraction. It is of interest that the upper end of the esophagus, closed by the cricopharyngeal sphincter, contains similar "cardiac" glands.

Another type of valvular mechanism, that is, the production of a flap valve as a result of the acute angle or incisura between the abdominal esophagus and the fundus of the stomach has also been described as of great significance in the closing mechanism (8). On the other hand, it is clear that the acuteness of this angle is not directly related to the presence or absence of reflux (11). The rôle of the incisura as an isolated factor is therefore difficult to evaluate and the description of flap valve action is not entirely satisfactory. It may be that the effect of this angle is related to the efficiency of application of an intragastric distending force to the center of the rosette canal. It should also be noted that a deep incisura is associated with a relatively long abdominal course of the terminal esophagus. The possible importance of this feature is described below.

Since intrinsic anatomical or physiological features do not appear to explain entirely the closing mechanism in the esophagogastric region, an extrinsic "diaphragmatic factor" presumably related to the "pinchcock action of the diaphragm" has been postulated. It is the thesis of this report that such a factor can be found in the hydrostatic features of this area if proper consideration is given to the abdominal portion of the esophagus. While there has been controversy as to the existence of any portion of the esophagus below the hiatus, there seems to be little question at present from studies with opaque markers and intraluminal pressure recordings that the terminal esophagus over a distance of 1 to 3 cm is within the high pressure abdominal compartment rather than in the thorax. It is difficult to prove that the point of respiratory reversal clearly seen on pressure curves corresponds exactly to the muscular margins of the hiatus since normally these may be rolled downward in a funnel arrangement around the terminal esophagus. From a functional point of view, this is of no great importance. The fascial prolongations from the muscle margins to the esophagus and stomach are multiple but the strongest of these appears to be the uppermost, attached not at the esophagogastric junction but 2 to 3 cm above this level. This superior layer of the hiatal fascia has been referred to as the phrenico-esophageal membrane. Studies with an opaque marker on the anterior margin of the hiatus (12) indicate that the level of the hiatus is considerably above the cardia and is often at or above the level of the top of the fundus of the stomach.

The hydrostatic relationships required to initiate and maintain a flow of fluid through the abdominal portion of the esophagus into the stomach are indicated in diagrammatic fashion in figure 2. The caliber of the abdominal portion of the esophagus is determined by the hydrostatic pressure within it, the circular tension in its walls and the hydrostatic pressure outside of it. These factors are related to each other in accordance with the law of Laplace as applied to a cylinder: the radius is equal to the tension divided by the difference in

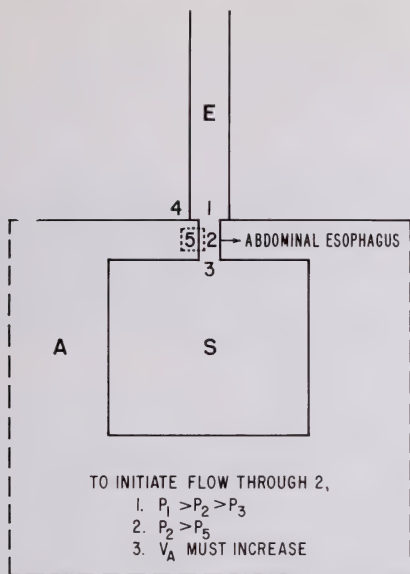


FIG. 2. The thoracic portion of the esophagus (E) is represented as entering the stomach (S) through a short relatively narrow canal (the abdominal esophagus) within the abdomen (A). The numerals indicate regions where pressures are important. The region indicated by 5 refers to the compressing effect on the lumen of the abdominal esophagus of extrinsic intra-abdominal pressure plus intrinsic contraction (muscular and elastic) of its walls. In order for fluid in the thoracic esophagus to enter the abdominal esophagus, the pressure head (P_1) must be sufficient to create a pressure (P_2) in the abdominal esophagus which will exceed the compressing pressure (P_5). Because of the sphincteric nature of the abdominal esophagus, this pressure (P_2) will ordinarily exceed the pressure in the stomach (P_3). The pressure head required to maintain a flow of fluid through the relatively narrow abdominal esophagus is greater than the pressure required to open it because of the Bernoulli effect (see text). In addition, since the abdominal contents are essentially not compressible, fluid cannot enter the abdomen unless the volume of the abdomen (V_A) as well as of the stomach is permitted to increase. If this does not occur, as soon as a small amount of fluid enters the stomach, intra-abdominal pressure around the abdominal esophagus will rise abruptly and collapse its lumen.

pressure (13) (Fig. 3). This difference in pressure between extrinsic and intra-luminal pressures is referred to as the transmural pressure. The requirement that the volume of the abdomen (as well as the volume of the stomach) be increased by relaxation of its walls is easily overlooked. Unless this occurs, extrinsic pressure would prevent the entrance of any fluid into the abdomen since, in the physiological range, the abdominal contents including the gas in the gastrointestinal tract are essentially not compressible. Under unusual

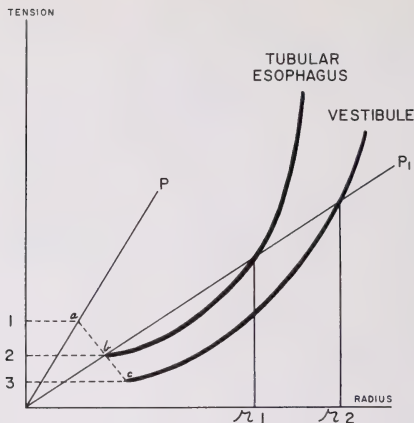


FIG. 3. Graphic representation of "filling curves" of the tubular esophagus and the vestibule or sphincteric zone. On the basis of a cylindrical configuration, the slope of the line joining any point to the origin is equal to the difference between the intraluminal and extrinsic pressures (law of Laplace) (13). If this transmural pressure difference were the same in the tubular esophagus and the vestibule (P_1), the radius of the tubular esophagus would equal r_1 and of the vestibule r_2 . If pressure in the tubular esophagus were reduced, a point is reached, (b), at which the increasing active muscular contraction of the wall cannot be counterbalanced by the decreasing elastic tension and, as a result, the lumen collapses completely (dashed line). Tension in the wall is then represented by ordinate [2]. The pressure at which this occurs has been referred to as the "critical closing pressure" (13) and the corresponding radius represents a minimum diameter of the (fluid-filled) lumen. The sphincteric nature of the vestibule is indicated by a higher resting tone [1] than would be expected from the continuation of the filling curve [3]. Putting this in words, the critical closing or opening pressure (P) of the vestibule is greater than it is for the tubular esophagus (P_1). Once opened, however, for a given transmural pressure, the radius of the vestibule is greater than the remainder of the esophagus. This is of special importance in the abdominal esophagus since a larger channel can be maintained with a given intraluminal pressure (above the opening pressure) despite the higher intra-abdominal pressure.

circumstances, a strong peristaltic contraction of the esophagus might eject fluid into the abdomen with sufficient force to stretch the walls of the abdomen from within. Under ordinary conditions, a voluntary or reflex relaxation of the abdominal wall is necessary. As indicated in figure 4, the physiological phenomena of deglutition are designed to satisfy these physical requirements.

It is of interest to examine the hydrostatic relationships after a flow of fluid is established. Since the difference between internal and external pressures is less in the abdominal esophagus than in the thoracic esophagus, the caliber of the abdominal esophagus is also somewhat less. According to Bernoulli's law, the hydrostatic pressure in the narrowed segment is less than in the adjacent wider regions in proportion to their cross-sectional areas. If, while fluid is flowing, intra-abdominal pressure is rapidly increased, for example, by a deep inspiration, the caliber of the abdominal portion of the esophagus begins to decrease because

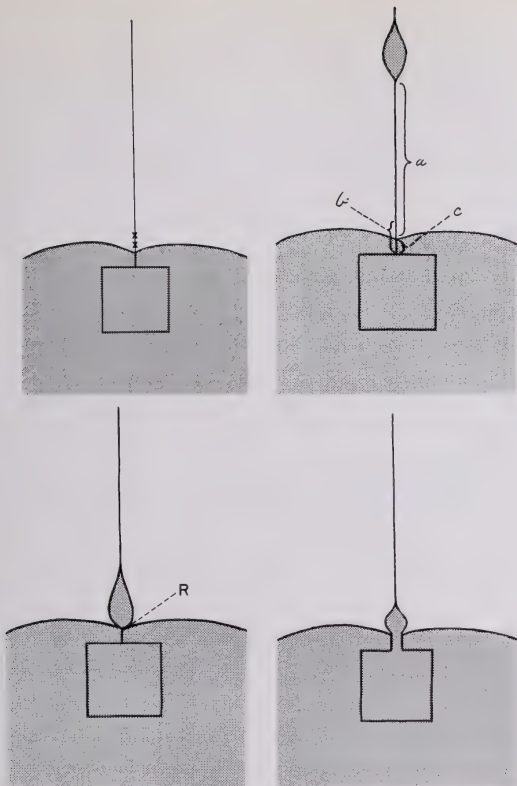


FIG. 4. Course of events during deglutition.

FIG. 4A. In the resting phase, the sphincteric action of the terminal portion of the esophagus produces the highest intraluminal pressure at and immediately above the hiatus.

FIG. 4B. As the bolus enters, the pressure throughout the thoracic esophagus (a) is increased while the sphincteric region (b) is relaxing. The pressure in the abdominal esophagus (c) is decreasing during this time.

FIG. 4C. The bolus of fluid has reached the level of the hiatus (R). This corresponds to the "point of respiratory reversal" found on intraluminal pressure tracings (4). The pressure head is adequate to induce the passage of the bolus into the abdominal esophagus and into the stomach but transient delay occurs until the volume of the abdomen can be increased.

FIG. 4D. As the diaphragm rises slightly and/or the abdominal wall relaxes, fluid enters the abdominal portion of the esophagus and flows into the stomach. It is possible to "prepare" the abdomen for the act of deglutition by lowering the level of the diaphragm prior to the onset of swallowing and then permitting it to rise as deglutition progresses. This can be done without any marked change in intra-abdominal pressure. When the bolus reaches the hiatus under these circumstances, the required volume will enter the abdomen promptly and no delay at the hiatus will be evident. This latter sequence of events corresponds to the phenomena described as occurring during "drinking" as compared with those seen during "swallowing" (4).

of greater extrinsic pressure. With diminishing caliber, the hydrostatic pressure within it due to flow decreases even further. A "vicious circle" is set up and the difference in pressure rapidly becomes insufficient to maintain any lumen at all, that is, the critical closing transmural pressure is reached. As long as deep inspiration is maintained, the volume of abdominal contents cannot increase and the abdominal esophagus appears to act as a "sealed-off" segment. This sequence of events corresponds to the "pinchcock action of the diaphragm" or, more correctly, "the pinchcock action of inspiration". The hydrostatic features appear sufficient to explain this phenomenon without requiring intimate application of the crura of the diaphragm or the phrenicoesophageal membrane to the terminal portion of the esophagus.

Pinchcock action of the diaphragm is a special example of the role of the abdominal portion of the esophagus as it is affected by changes in intra-abdominal pressure. If this segment were not present, an increase in intra-abdominal pressure due to inspiration or exertion requiring contraction of the abdominal muscles or pelvic floor would be directly transmitted to the gastric contents and serve as an additional distending force acting on the terminal esophagus above the hiatus (Fig. 5A). Normally, however, *i.e.* in the presence of an abdominal portion of the esophagus, the increased pressure is also simultaneously and uniformly applied around the abdominal portion of the esophagus (Fig. 5B). The increased intragastric pressure is therefore automatically compensated for by the increased extrinsic pressure acting to prevent opening of the abdominal esophagus. The distending force is therefore independent of intra-abdominal pressure. Intrinsic sphincteric activity of the terminal esophagus which is sufficient to counteract the negative intraesophageal pressure and any increment in intragastric pressure produced by tension of the stomach wall is therefore adequate to prevent reflux. This description fits nicely with the location of the high pressure zone, namely, a short distance below and a somewhat greater distance above the hiatus (3). When intra-abdominal pressure is progressively increased, a point is reached at which relaxation of the sphincteric area occurs abruptly in order to permit reflux and relieve discomfort.

It is possible to increase intragastric pressure independently of intra-abdominal pressure by marked distention of the stomach, particularly with gas. Under these circumstances, the distending force on the abdominal esophagus may be sufficient to induce belching or vomiting, thereby re-establishing more stable and more comfortable pressure relationships. It is of interest to note that, during these phenomena, the abdominal portion of the esophagus appears to become physiologically temporarily abolished.

The application of the hydrostatic features to the inverted or Trendelenburg position is of special importance since this position is often used as a test for reflux. The fact that reflux of gastric contents into the esophagus does not normally occur in this position is the classical observation from which the deduction that a closing mechanism in the esophagogastric region is present was made. The hydrostatic factors involved in this position are demonstrated diagrammatically in Fig. 6. It is clear that, because of the abdominal esophagus,

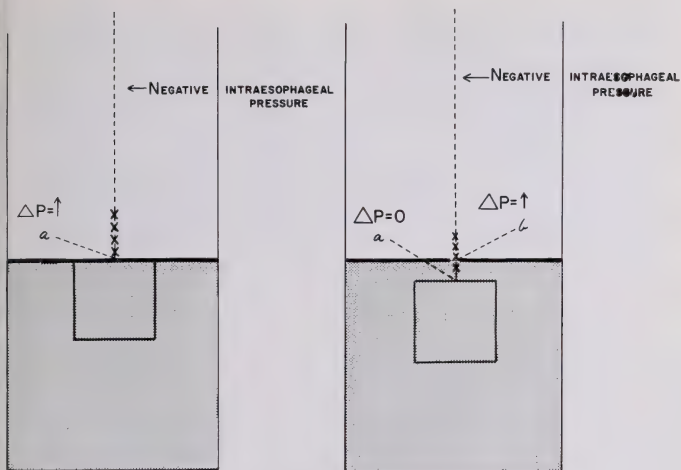


FIG. 5A. A fluid-filled container with elastic walls within a larger fluid-filled container is present immediately below an air-fluid boundary. The dashed line represents a collapsible tube in which a pressure equal to the negative intraesophageal pressure exists. Under these circumstances, at point (a), an active or sphincteric closure equivalent to the difference between intragastric and intraesophageal pressure (ΔP) is required to prevent reflux. The intragastric pressure below point (a) is equal to the intra-abdominal pressure at this level plus the pressure created by tension of the gastric wall. This gastroesophageal pressure difference in the erect position ordinarily varies between 5 and 15 cm of water, approximately the same as the pressure barrier which can be created by the intrinsic sphincter in the terminal esophagus. If, however, intra-abdominal and thereby intragastric pressure is increased above these levels, the full increase would have to be counterbalanced by more active contraction of the terminal esophagus. If this is not possible, reflux will occur.

FIG. 5B. If a small portion of the tube extends below the surface, no hydrostatic pressure difference and no distending force due to intra-abdominal pressure exists at point (a). Any increase in intragastric pressure due to an increase in intra-abdominal pressure is counteracted by a similar increase in extrinsic pressure on the abdominal esophagus.

intra-abdominal pressure effectively completely surrounds the stomach and the purely hydrostatic features are even more favorable for the prevention of reflux than in the erect position (Fig. 7A). No greater intrinsic sphincteric activity in the terminal esophagus is required with the patient in this position than in any other. If the abdominal portion of the esophagus is absent (Fig. 7B), a very unfavorable arrangement for the prevention of reflux exists hydrostatically since, in effect, a pressure head equivalent to the height of the abdomen is present at the esophagogastric junction. This corresponds to the clinical condition of "chalasia" seen particularly in newborns in whom reflux occurs with the smallest increase in intra-abdominal pressure. In contrast, the presence of a small sliding hernia is less likely to be associated with reflux (Fig. 7C) since the herniated

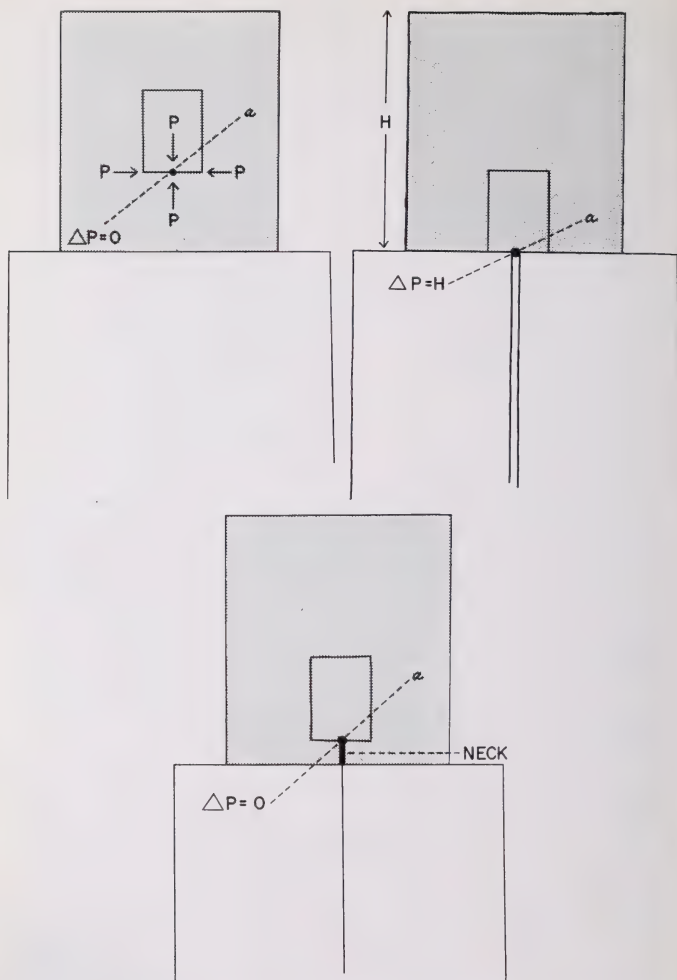


FIG. 6. Hydrostatic factors in the inverted position.

FIG. 6A. The diagram indicates a large fluid-filled container supported on a table. Within this large container, there is a smaller container containing similar fluid, with elastic walls which transmit hydrostatic pressures freely. In accordance with Pascal's law, the pressure

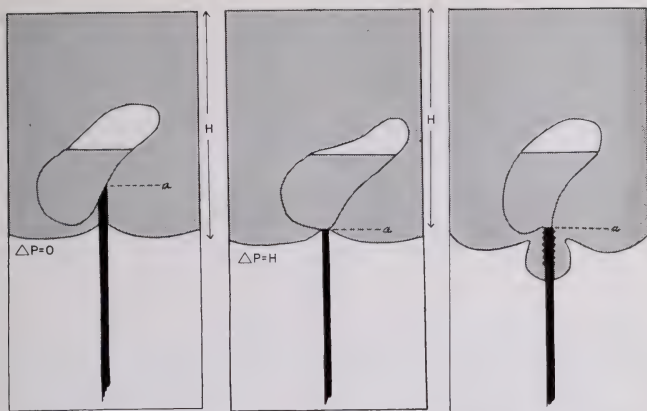


FIG. 7. Diagrams to indicate pressure relationships in the Trendelenburg position.

FIG. 7A. Under normal circumstances, a significant length of abdominal esophagus is present and the hydrostatic forces are the same as those indicated as figure 6C. The pressure difference (ΔP) due to hydrostatic factors is zero at point (a).

FIG. 7B. If the abdominal portion of the esophagus is absent, a pressure head equal to the full height of the abdomen (H) is exerted at point (a) and free reflux into the esophagus is likely to occur. This arrangement corresponds to the condition described as "chalasia".

FIG. 7C. In the presence of a small sliding hiatus hernia, a sac-like protrusion of abdominal fascia extends into the mediastinum around the herniated abdominal esophagus and the herniated portion of the stomach. If this fascia is not excessively stretched intra-abdominal pressure (H) is exerted on the herniated structures and, in effect, a "neck" surrounded by high pressure is present. If the collapsed or empty herniated portion of the stomach and esophagus can maintain a contraction sufficient to counterbalance the difference between intragastric pressure due to tension of the gastric wall and intraesophageal pressure, hydrostatic pressure will maintain closure at point (a) and throughout the neck. In the presence of a large hernia, the maintenance of the contracted state of the herniated portion of the stomach is less likely and intra-abdominal pressure extends into the mediastinum for a relatively shorter distance beyond the hiatus.

viscera are still subjected externally to intra-abdominal pressure. With a large hiatus hernia of the sliding type, the effects of intra-abdominal pressure may not completely surround the sac but be confined to the region of the hiatus, that is, to the neck of the hernial sac. This neck may still serve to some extent in a

at (a) is the same in all directions; the difference in pressure or ΔP is 0 and no pressure head exists. As a result, fluid does not leave the small container even though the flexible side walls of the larger container might permit it.

FIG. 6B. If the smaller or inner container is brought down to the table top, a considerable head of pressure, equal to the full height of the outer container (H), is present at point (a). If an opening were present at this point, fluid would flow out freely and the side walls of the outer container would collapse as the inner container empties.

FIG. 6C. If, however, the smaller inner container is brought a short distance above the table top, the hydrostatic pressure relationships return to those demonstrated in figure 6A—that is, if an opening were present at (a), no fluid would leave the container since the pressure head is zero. An elastic tubular "neck" connecting point (a) to the tube below the table would fail to fill since there is no intraluminal distending force. Pressure on the outside of the neck is the same as the pressure inside and is greater than the pressure in the small container. The "neck" represents the abdominal portion of the esophagus, the large fluid-filled container the abdomen and the small container the stomach.

fashion similar to the abdominal esophagus and reflux under moderate stress may be prevented in the region of the hiatus. This corresponds to the clinical finding (1) that, in many patients with sliding hiatus hernias, reflux into the hernial sac and into the esophagus does not occur in a moderately inverted or Trendelenburg position.

The presence of a gas bubble in the stomach does not alter the hydrostatic relationships described above. In the erect position when a column of gas is present below the level of the cardia (Fig. 8), the hydrostatic effect is to increase intragastric pressure at the level of the cardia by an amount equivalent to the height of the column. This arises from the fact that the pressure in the gas

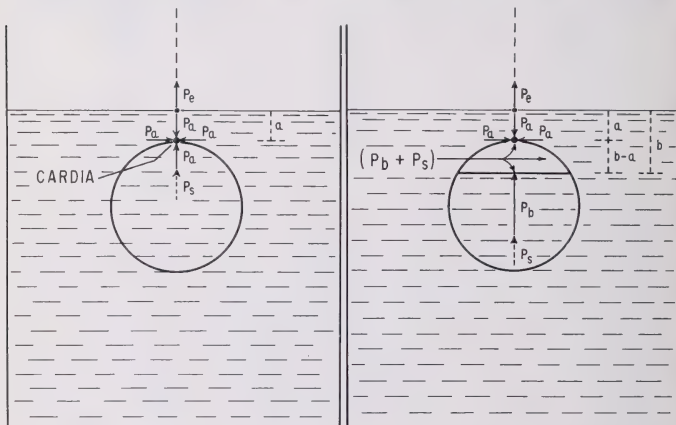


FIG. 8. Pressures related to gastroesophageal reflux.

FIG. 8A. Stomach filled with fluid. The intra-abdominal hydrostatic pressure at the cardia, P_a , is exerted in all directions--from each side on the walls of the abdominal esophagus, from above, and from below via the fluid gastric contents. (The total intra-abdominal pressure will be higher than the hydrostatic pressure to a degree dependent on the state of contraction of the diaphragm, abdominal wall and pelvic floor. This contribution to intra-abdominal pressure may be considered to be the same throughout the abdomen to a first approximation and therefore is not pertinent to the present argument). The additional increment contributed to intragastric pressure by tension in the gastric wall is represented by P_s . The negative intraesophageal pressure is indicated by P_e . Pressure favoring reflux is the difference between $(P_a + P_s + P_e)$ and (P_a) , or simply $(P_s + P_e)$ since P_a cancels out. Active contraction in the terminal esophagus sufficient to counteract $(P_s + P_e)$ will prevent reflux.

FIG. 8B. Air and fluid in the stomach. The pressure throughout the air column is equal to the pressure at the fluid level (P_b) due to transmission of intra-abdominal pressure to the gastric contents plus the increment due to gastric tension (P_s). The pressure favoring reflux is the difference between $(P_b + P_s + P_e)$ and (P_a) , or $(P_b - P_a + P_s + P_e)$. $(P_b - P_a)$ is the same as (P_{b-a}) , i.e., is equal to the pressure created by a height of fluid equal to the height of the air column. This represents the additional contractile force required in the terminal esophagus to prevent reflux over and above that necessary when no air is present. Since the gas bubble in the stomach rarely extends any great distance below the cardia, this additional force is ordinarily not significant.

collection is the same throughout and is equal to the pressure at its inferior boundary. Under ordinary circumstances, the amount of gas in the stomach below the level of the cardia is not significant.

From a theoretical consideration of the physical factors involved therefore, it would appear that the "diaphragmatic factor" recognized to be part of the closure mechanism in the esophagogastric region may be attributed to the action of hydrostatic forces on the intra-abdominal portion of the esophagus. It is not necessary for these physical relationships to hold that this portion of the esophagus be of any great length since the essential feature is the fact that the stomach is completely surrounded and exposed to intra-abdominal pressure. The reports that simple gastropexy (14) or pneumoperitoneum (15) may be effective in the treatment of hiatus hernia are consistent with these findings.

SUMMARY

Factors of accepted importance in the closure mechanism at the esophagogastric region include intrinsic sphincteric activity of the terminal 2 or 3 cm of the esophagus, the rosette canal, and probably the oblique entry of the esophagus into the stomach.

The accepted factors, however, do not appear to explain this mechanism entirely satisfactorily since it can be demonstrated that reflux of gastric contents into the esophagus may not occur even though intra-abdominal pressure is increased markedly.

This paper presents considerations of the hydrostatic factors involved, particularly as applied to the rôle of the abdominal portion of the esophagus. It would appear that because of the presence of the abdominal esophagus, the barrier pressure required to prevent reflux is independent of intra-abdominal pressure and independent of the position of the patient.

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LATE SURGICAL FINDINGS IN A TRAUMATIZED KIDNEY. A CASE REPORT

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It is unusual to be able to surgically inspect a kidney some time after an obvious traumatism. For this reason the following report is thought to be of interest.

CASE REPORT

M. S., a boy of eleven, was first seen on January 12, 1959, with a history of occasional pain in the left loin and intermittent episodes of gross, total hematuria for the past three months. One year previously he had sustained a ruptured left kidney after being struck by an automobile. At that time the intravenous pyelogram showed a rupture through parenchyma with a small peri-renal hematoma. His condition was good; his hematuria subsided after a month of bed rest in a hospital. No surgery was performed. Since March, 1958 a series of intravenous pyelograms have shown a normal right upper urinary tract. There was slight dilatation of the left kidney and a possible filling defect in the pelvis (Fig. 1). His past history was negative except for the usual childhood diseases. On examination blood pressure was 100:70. His urine contained no albumin or sugar but on microscopic examination many blood cells were present. Physical examination was completely negative. Blood urea nitrogen and complete blood count were normal. The kidneys were not palpable and were not tender. A retrograde pyelogram was suggested and performed. Cystoscopy revealed the bleeding to be from the left kidney. X-rays demonstrated an irregular, oval filling defect in a slightly dilated pelvis and a stricture of the ureter at the pyelo-ureteral juncture (fig. 2). The patient was admitted to The Mount Sinai Hospital on February 23, 1959, and the following day an exploratory operation of the left kidney was carried out. The perinephric fat was found to be fibrotic and there were marked fibrous adhesions around the kidney and upper ureter. The kidney itself appeared to consist of two completely separated parts, namely an upper and lower pole united by the pelvis and calyces and a very small amount of renal tissue in the central portion. The kidney was mobilized and then the ureter was identified and traced upwards to the pelvis. During this process peri-ureteral and peri-pelvic fibrous tissue was excised. After this procedure the upper portion of the ureter which had been narrowed on the pyelograms now expanded to a normal calibre. The pelvis and pyelo-ureteral juncture were opened between sutures and the kidney explored with a stone forceps. Although the negative shadow had been in the pelvis on repeated x-rays a uratic appearing stone about 15 by 8 by 4 mm was extracted from the uppermost calyx. The pelvis was closed with fine atraumatic sutures; the wound was drained and closed in the usual manner. It

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Fig. 1. Intravenous Pyelogram. Right upper tract normal. Left kidney suggests filling defect in pelvis, also narrowing at pyelo-ureteral junction with moderate pelvic and calyceal dilatation.

should be noted that there was no constriction or narrowing of the renal vessels. The chemistry of the stone was reported as showing uric acid with some calcium oxalate and calcium phosphate. The postoperative course was uneventful and on discharge an excretory urogram showed good function of the left kidney without significant dilatation. The patient left the hospital on the ninth post-operative day. He has been followed since his discharge from the hospital. He is well and active. Thirteen months after surgery the urine is microscopically negative and



FIG. 2. Left Retrograde Pyelogram. Filling defect in pelvis; stricture at pyelo-ureteral area.

on excretory urogram there is prompt, bilateral visualization with relatively normal upper tracts and no left sided dilatation (Figs. 3 and 4).

It is obvious from the surgical findings that this patient suffered an almost complete laceration of the left kidney, extending from the cortex to the pelvis. It is interesting to speculate on the course of this case had primary surgery been performed. Surgery was not done because the patient's general condition



FIG. 3. Intravenous Pyelogram. Five weeks post-operative. Calculus absent from left kidney.

remained good under careful observation and the pyelographic changes were not too abnormal. If the patient had been operated on it is possible that the kidney might have been sacrificed or possibly the two parts of the kidney might have been re-sutured with a danger of secondary hemorrhage. Certainly the post traumatic formation of the stone would not have been prevented since this stone probably formed around a small blood clot or aggregation of fibrin. It is also questionable whether the marked peri-renal and periureteral fibrosis which



FIG. 4. Intravenous Pyelogram. Seven months post-operative. No dilatation; no evidence of calculus.

occurred would have been prevented by such a primary operation. It should be noted that at no time was there any evidence of infection of the urinary tract.

SUMMARY

A case is presented of an eleven year old boy treated conservatively for a partial transverse laceration of the left kidney who was operated upon one year later for a pelvic stone causing hematuria and a pyelo-ureteral narrowing due to extra-pyeloureteral fibrosis. The patient has apparently been cured by the operative procedure.

CONCEPTS OF NORMAL HEARING

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INTRODUCTION

To try to describe what is normal in human behavior or function is often an elusive undertaking; a brief definition seems inadequate to encompass the manifold reactions of human audition. We accept our reception and our responses to sound without thought unless something occurs to interfere with this.

To be able to hear something requires a sound source, a stimulus, and a sensory receptor. We may eliminate, tentatively, mechanical receivers which do not have physiological and psychological elements.

The amount of sound in one's environment is undoubtedly enormous in quantity and in variety. What is recognizable to us must be a fragment of this total mass, because we possess a receptor organ capable of responding only to a tiny part. Here may lie a clue why a very small hearing loss in some people may be of greater discomfort than might be expected.

THE SOUND WAVE

Physical sound starts off from a source which produces an air wave in the atmosphere, so often compared to the water wave which is formed when a pebble is dropped into a pail of water. The water wave can be produced also by blowing air over the surface of the water, or rocking or shaking the bucket. The wave results from a variety of stimuli. The force of the wave produced, acoustical or aqueous, depends on the initial energy of the stimulation. The greater the initiating effort, the higher and more vigorous is the wave, which can be described as the intensity of the wave. Acoustically, the more vigorous the wave the louder is the sound to the ear; the less vigorous wave movements are appreciated as softer sounds. A wave action which is ever so slight may be too weak to move, to stimulate, the structures of the ear and thus will not be heard.

INTENSITY (VOLUME)

A measurement of intensity is indicated by the term decibel. Volume is the subjective experience. The decibel expresses the energy and this unit is essentially a statement of so much physical sound pressure. The decibel is a logarithmic expression more easily manipulated clinically than other equivalent measurements. A great number of decibels is interpreted subjectively as a loud sound, the fewer the number of decibels the softer is the sound. Audiometrically, the range for humans starts at about -15 decibels or -10 decibels, and extends to well above 100 decibels. These very high levels can be, and frequently are, injurious to the auditory neural components.

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FREQUENCY (PITCH)

Another characteristic of the wave is the time in which it moves. How many times, how often does it beat in a second, how many waves occur in one second. Frequency is a physical factor, pitch a subjective one. The average unimpaired young adult ear can hear a range of frequencies from about 30 cycles (beats) in a second to about 12,000 to 15,000 cycles per second. The speech range is within 6,000 cycles per second.

Some ears can hear a stimulus a little slower than 30 cycles per second. Some ears can hear up to about 18,000 or even 20,000 cycles per second. Waves beyond either end of this segment of the spectrum are rarely heard by the human ear. The dog's hearing spectral range is wider, to about 30,000 cycles per second and more; and that of the bat's is still wider, to over 50,000 cycles per second. The supersonic zone of a million cycles per second is entirely inaudible, but the energy of ultra sonic waves can be harnessed in ways other than auditory.

We now have two basic factors: a) power, volume, intensity; b) rate, pitch, frequency. For a stimulus to be heard as sound, both intensity and frequency must function within discreet magnitudes. Beyond these magnitudes the physical phenomenon of wave movement will be present but will not be audible and it will not be sound. These elements are influenced by, amongst other things, the density of the environment in which the wave exists, whether it be gas, as air, a fluid or a solid.

MEASURING HEARING

Ordinarily the qualitative and quantitative testing of hearing is performed under normal atmospheric conditions in the quiet environment of a sound-treated room. Several frequencies are explored. Usually the testing is accomplished either by using tuning forks or with audiometers. The metal tuning fork is of simple construction. The audiometer consists of a complex of electric circuitry with an air conductor receiver and a bone oscillator. Usually only seven or eight frequencies out of the entire human auditory spectrum are tested. The frequencies are pure tones—all vibrations of each frequency are of the same rate per second. These are 125 cycles per second, 250 cycles per second, 500 cycles per second, 1000 cycles per second, 2000 cycles per second, 4000 cycles per second, 8000 cycles per second. These are octaves of the key of "C", free of harmonics.

Tuning forks are calibrated in frequencies of pure tones, rarely in decibels. Audiometers are calibrated both in frequencies of pure tones and in decibels.

Audiometric testing of hearing includes measuring the activity of the middle ear and neural pathways by air conduction, and the activity of the neural pathways alone, by bone conduction. The air conductor receiver is applied to the auricle; or the bone oscillator is held against the mastoid process. The least number of decibels required at a frequency just barely acoustically perceptible to a subject becomes the threshold hearing at that frequency. Acceptable normal thresholds are within the 20 decibel level. The relatively ideal normal threshold is at the zero decibel level. Many people have this acuity. Some people have even

greater acuity of hearing with thresholds in the minus range. Deviations from and above the normal range are indications of hearing defects and the configurations of these deviations express varieties of pathology.

Pure tone hearing is not the usual daily acoustic experience. We are bombarded constantly by complex compositions of frequencies. When these forms are considered pleasant, or not objectionable, they are described as sounds; if unwanted, they become noise. This distinction may be only a social or a psychological one.

SPEECH AND SPEECH HEARING TESTS

Our most important sound signal is speech. Words contain many frequencies which are vocalized at different intensities. In English most vowels are composed of the lower frequencies and many of the consonants contain the higher frequencies. The vowels are more highly powered than the consonants; the latter often tend to fade away at the end of words and at the end of sentences. Under adverse listening conditions even a normal ear will be unable to respond accurately to parts of words or even to some whole words, or may mistake one word for another.

In order to probe the speech hearing efficiency of an ear two test series of words are in use. One series is composed of calibrated bisyllabic words—Spondees—with which the speech reception threshold is measured. The speech reception decibel threshold may or may not be the same as the pure tone air conduction threshold.

The second series of words is composed of monosyllables, phonetically balanced, wherein the understanding of each word depends primarily on the ear's ability to hear and to analyze the higher frequencies of which the consonants are composed. Some poor hearing ears for spondaic words may have normal scores for these difficult phonetically balanced words. Other impaired ears with approximately normal spondaic speech reception thresholds may demonstrate a significant loss for the discrimination of phonetically balanced words. Some ears which perform relatively competently in a quiet condition of testing may show very poor responses in a controlled noisy testing situation.

SPEECH VARIABLES

Speech hearing is influenced by innumerable factors such as the nature of the speech production and the condition or situations into which it is introduced. Some speech varieties are those of children beginning to talk, the female and male voice, singing voice ranging from bass to soprano, whispered voice, theatrical speech, laryngectomy speech, the speech defects of impaired speech organs such as hoarseness associated with laryngeal disturbances, paralysis, or malfunction of speech organs, the integrity of the palate, pharynx, tongue, teeth, lips, and nasal structures. Speech is modified by local geographical influences and habits. The spoken English of the New Yorker, of the South, Southwest, and West vary considerably. The varieties of English of Great Britain and of the Caribbean Area are still different. The speech of the tobacco auctioneer is an example of the unfamiliar. Speech is altered or changed by foreign accents, enunciation and pronunciation.

VOICE AND HEARING

Speech elaboration is quantitatively restricted to the physical and physiological limitations of the organs of voice production. There appears to be a harmonious relationship between the ability of the ear to hear comfortably and the speech apparatus to perform effortlessly, under ordinary conditions. A small alteration in this harmony because of some defect or alteration in the sending system or in the receiving system will require the expenditure of additional effort on the part of both systems to accomplish successful communication. Reception of phonation over a distance as in an auditorium or in a noisy environment demands greater conscious effort in listening than does ordinary *vis-a-vis* conversation.

KINDS OF SOUNDS

Sounds and acoustic signals, in general, may be divided into two groups, natural sounds and manufactured sounds. Both appear in endless variety.

Natural sounds fall into two divisions, a) biologic and b) nonphysiological. Examples of biologic sounds are the calling of birds, hissing of snakes and insects, roaring, barking, braying, cooing, "chirping" of crickets, heartbeat, chest sounds, human voice, humming, whistling, and singing. Examples of nonphysiologic sounds are thunder, waterfalls, rustling of leaves in the wind, rain falling on the ground, the roar and rumble of the surf, the crackling of fire and many others. It is significant that with the rarest exceptions none of these natural sounds when heard is of such a magnitude as to be injurious to the ear. None will cause deafness.

The manufactured, man invented, sounds are in the second group. Again, the variety is almost infinite and of a different kind. Music produced by stringed, percussive, and wind instruments are welcome sounds. Communication as Morse code, radio, telephone are further evidences of man's ingenuity to overcome obstacles and shape his world. But other sounds—noises—are of another order. The day in and day out environmental din of street traffic, horns, screeching of brakes, sirens, the rattling of windows, slamming of doors, ringing of bells, cackling of typewriters, the rumble of roller skates, the humming and whining of motors continuously bombard us and tend to tire us. Of an acoustically injurious magnitude are the noises of industry and of war. Pneumatic hammers, drills, pile drivers, pumping machines, engines all generate excessive high sound pressures to levels which can produce permanent damage to the auditory neural structures. The noises of explosives and weapons, artillery, rifle fire, bombs, jet engines, blast and concussion are baneful, deleterious and detrimental.

Such noise is wasted energy and injurious to human tissue. It is useless and valueless.

MIDDLE EAR

The contrast between the energy levels of natural sounds and of invented sounds may suggest something of the physiology of the mammalian middle ear other than generally accepted concepts.

It would appear reasonable to assume that the neuromuscular functions

within the middle ear could serve to increase acuity of hearing. Mammals living in their natural state for tens of thousands of years do not require a protective mechanism within the ear to defend the neural otic apparatus from high intensities of sound to which they could never have been exposed. A neuromuscular system might have been incorporated in the tympanum to sharpen hearing, in order that terrestrial animals abiding in their habitat would be able to detect the sounds of distant predatory enemies, or to hear sounds emanating from sources of food. When one considers that the jungle by day and night handicaps vision and that olfaction may be limited and circumscribed, acute hearing can become paramount as a means of feeling or touching at a distance, to recognize the presence of enemies, kin, and food. At home one's dog repeatedly announces the presence of guests even before the door bell signals their arrival.

It seems improbable that the human middle ear, with its delicate ossicles, ligaments, and tiny muscles, could have been basically designed millions of years ago in anticipation of the inevitable development of the industrial revolution with its awful noise. It is unlikely that the tympanum is a bulwark to protect the auditory neural elements from dangerous and injurious volumes of sound. There is evidence that a sudden burst of damaging noise produces an almost instantaneous effect, causing both deafness and tinnitus. This high intensity acts so rapidly that the intra-tympanic muscles cannot react so promptly and effectively and be of significant protection. Rather, it would appear that these muscles enhance the acuity of hearing for signals of minimal intensities. It seems functionally reasonable that just as an animal cocks his pinnae, by contraction of the extra auricular muscles to bring in more sound when he is alerted, so will he call upon the tympanic muscles.

When the human makes a deliberate effort to hear something which is soft and distant he tones up much of his entire musculature. Skeletal muscles tense, sphincters are tightened, respiration is depressed or suspended. The head is held rigid by the cervical muscles. Jaws become lightly clinched. The tongue and palate movements subside, and the eyelids and eyes tend to become fixed. It seems apparent that the tympanic muscles must contract also. If we assume that these muscles take up some slack in the ossicular chain then threshold acoustic stimuli will more readily move a more sensitive and more delicate system and thereby transmit weaker impulses to the vestibule of the inner ear.

BINAURAL NORMAL HEARING

There is another dimension of hearing. This is the hearing experience of listening with two competent ears as compared to listening with one competent ear and one defective ear. Binaural hearing permits one to localize the place where a sound originates. Space, depth, and distance can be judged. Binaurality implies stereophonic hearing.

Binaural hearing permits one to select from an environment flooded with many acoustic signals those to which he wants to listen. In a noisy social gathering one can listen to a single source or conversation and tune out undesired competing signals.

Furthermore, with binaural hearing one can tune out conversation or other

social sounds in one's environment and bring in a more distant signal. Eavesdropping at restaurants, theaters, or parties, are common experiences of this selectivity.

Binaural hearing preserves the ability to discriminate speech in noise. Enough speech can be absorbed by both ears so that recognizable information can be transmitted to the acoustic brain centers.

Binaural hearing permits one to listen to sounds emanating from either side of the mid line, without requiring a change in position of the head or body. Several signals can be absorbed and registered efficiently and effectively by the listener. Some occupations require the individual to listen to two telephone receivers, or to two different code signals through two receivers, each transmitting a different message. A person can carry multiple conversations in such situations. Mobility in listening is achieved with binaural hearing. One can sleep on either ear with the other ear "opened," as it were. With binaural hearing one picks up tiny acoustic clues easily.

MONAURAL HEARING

The individual with monaural hearing has lost most of this flexibility. He cannot localize, he is unable to select one set of signals contending with unwanted other signals. He misses many of the jokes in the theater because he cannot separate the laughter of the audience from the speech of the entertainer. He is unable to tune in or out, to select what he wishes to hear. He must turn his head and often his body to get in the beam of the conversation or signal. If he sleeps on his good ear, he fails to hear the alarm clock, the telephone or the doorbell ring, the baby cry, and a host of other signals. Also, he has lost the ability of listening accurately at a distance.

Monaural hearing is inadequate in many life situations and occupations. If the "monauralist" walks across traffic with a defective ear toward the oncoming cars he may not hear the warnings. This hazard occurs in many occupations, such as railroad track walkers, laborers, workers in noisy shops. Often simple directions or instructions are missed in such noisy settings.

Other handicapping situations involve drivers of vehicles. If the left ear is the competent one the driver hears the traffic noises but not what is said by the passengers. If the right ear is the competent one he often fails to hear many signals and warnings coming to his left side. Such problems and examples are described by taxi and bus drivers, men working in assembly lines, as well as those in sedentary occupations attending interviews and round table conferences. The occupations and vocations threatened by a hearing loss of one ear are innumerable. Musicians and orchestra conductors, judges and lawyers, operating room nurses, waiters and bartenders are some of an endless list whose monaural loss creates a handicap.

MUSIC: AN ACOUSTIC EXPERIENCE

Music is another area of human behavior which distinguishes mankind from his mammalian relatives. We can sing, whistle, purr and growl as do other animals. We can snap, clap, click, thump, and beat also. But we have designed

tools with which we can make other and new sounds. We can combine these sounds into relationships which we call music.

A written and readable system of notation has evolved which can be translated and transformed by equipment into acoustic form. Each class of sound producing instruments possesses its own acoustic spectrum and harmonics. The frequency range of the entire orchestral machine extends well into the upper end of the human auditory spectrum.

A single audible note produced by a musical instrument carries with it its overtones and harmonics. Contemplate the acoustic phenomena of vocal and instrumental soloists, quartets, ensembles, choral groups. Consider the range and variety, the hugeness of the acoustical product of a fully complemented orchestra, of an operatic company. Music, desirable, exciting, magnificent, expresses human emotion of the highest order. Music is a measure of the uniqueness of human intellectual and emotional acoustic behavior.

AUDITORY MEMORY

Auditory memory can store away many kinds of acoustic experiences. Vocal mimicry is one kind. Mimicry is often observed in entertainment in the theater. Some actors render impressions of their colleagues, copying their voices and inflection. The imitation is just barely distinguishable from the authentic, yet the ear and memory recognize the similarity and the differences.

The sophisticated listener of music remembers and is able to distinguish several characteristics in voices and instruments, and performances can be compared and evaluated. Expressions such as "she was in good voice"; "He flattened the high notes"; "The tone of this instrument is superior"; and others reflect the ear's tuning ability for exactness of note as well as the awareness of volume of modulation and innumerable other characteristics.

In hearing, memory and familiarity play a part. Obviously we recognize the voices of family and friends. We receive a phone call and the conversation starts without any preliminary introduction. The familiar listener invariably recognizes the speaker by the unique distinctiveness of that one voice. Not only is the ear able to register particular qualities of the voice, but the cerebral acoustic memory centers are able to make certain identifications. This kind of memory includes songs, poems, and tales heard and learned in our childhood, which we can remember and identify after many years.

PSYCHOLOGICAL FACTORS

Our emotions and psychological attitudes influence our hearing, what we hear, and how we hear. Sometimes we don't hear what we do not want to hear. Sometimes we hear or think we hear something other than what was said. Sometimes we hear the silent phone or doorbell ring. Sometimes we hear but delay our responses or reply, because of some psychological influence. In psychiatry it is recognized that patients often hear only what they want, and reject that which they wish to deny.

We enjoy hearing certain voices or sounds and cringe and shiver at others,

such as chalk scratching across a blackboard. A baby responds to the warmth and love of a maternal voice. The child recognizes authority in the parental command. We stop with a traffic cop's whistle, and with the fire siren. Irony, sarcasm, humor, sympathy, anger, disgust, regret, grief, sorrow, anguish, pain, disappointment, sincerity and insincerity, joy and gaiety, humility, arrogance, tenderness, love are voiced and heard, and we react both to the word and its mood.

SUMMARY

How can we estimate the socio-economic amount of a hearing loss? Would a certain arithmetic quantitative loss of hearing for a 17th century and 20th century man be the same handicap socially and economically? Is a certain loss of hearing of the same value for a music critic, for a drama critic and for an art critic?

Can we estimate a percentage loss of hearing? Medico-legally certain firm answers may be required to meet that situation. However, in a broader sense a percentage loss of hearing is a meaningless number. Can we estimate the material, emotional, intellectual, and psychological costs of any hearing loss? Hearing losses vary from minute and asymptomatic to total deafness. No period of life is spared, from the newborn infant to the aged. Not only do the acoustically handicapped suffer but so do their normal hearing family, friends, and associates. No one really escapes some of the difficulties created by deafness.

The ear is truly a remarkable organ; microscopic in size, enormous in its response, economical in its physiology. An effort has been made to describe rather than define some ingredients which may contribute to a concept of normal hearing.

MITRAL STENOSIS; ITS SURGICAL CORRECTION. AN ANALYSIS OF 42 CASES

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The purpose of this paper is to present a review of mitral stenosis, with emphasis on pathophysiology, indications for commissurotomy, and the surgical techniques involved. An analysis of 42 cases operated at The Mount Sinai Hospital between April 1957 and October 1958 is included.

THE NORMAL MITRAL VALVE

A large anteromedial (or aortic) cusp or leaflet, and a smaller posterolateral leaflet, with their chordae tendineae and papillary muscles, constitute the mitral valve. The posterior or minor leaflet is attached by fibrous tissue (the mitral "ring" or annulus) to the left ventricular wall, and is continuous also with the endocardium of the left atrium; the basal aspect of the posterior leaflet has a direct attachment to the left ventricular myocardium. The anterior leaflet also is continuous with the endocardium of the left atrium, and with the aortic root and with portions of the left and posterior cusps of the aortic valve. Thus, the anterior leaflet forms the lateral aspect of the outflow tract of the left ventricle, separating it from the mitral orifice and directing the blood into the aorta (1, 2).

The leaflets closing the mitral ring are like two half-parachutes crowded together, one much larger than the other. During the first phase of ventricular systole (the phase of isometric contraction) the blood in the left ventricle balloons out the parachute-like leaflets from below, not only filling the mitral orifice, but causing the margins and occluding surfaces of the leaflets to be in apposition over a large area. Effecting a tight closure at the basal attachments of the leaflets are the two commissures, anterolateral and posteromedial. Valvular tissue bridges the two leaflets at the commissures.

The chordae tendineae attached to the anteromedial cusp are fewer than those attaching to the posterolateral cusp and are grouped, in about 50 per cent of instances, into two large bundles which attach themselves to each end of the undersurface of the free border of the cusp. The chordae of the posterolateral cusp are more numerous, shorter, and widely spread over the undersurface of the free border of the cusp (3). These differing anatomical characteristics of the two leaflets and of the chordae assume great significance in the surgery of the mitral valve.

In order for the valve to function properly, the leaflets must be intact and undistorted; they must be larger, when in apposition, than the orifice; sufficiently mobile to allow unrestrained apposition of one against the other; and, when in apposition, they must be restrained by the chordae tendineae and papillary mus-

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cles from everting into the atrium beyond the level of the optimal contact of closure (4).

PATHOGENESIS OF MITRAL VALVE DISEASE

Early in the course of rheumatic valvulitis, minute fibrin clots are deposited on the surface of the inflamed cusps, particularly the areas which come into apposition during ventricular systole. Similarly, platelets and fibrin are deposited on the chordae and papillary muscles. Repeated deposition of fibrin, with subsequent organization, results in fibrous thickening of these structures, often with varying degrees of calcification. Progressive encroachment on the commissures by fibrous tissue reduces the size of the valve orifice. Contraction of the scar tissue leads to distortion and loss of valve substance; if pronounced, an incompetent valve may result. A similar process involves the chordae tendineae and papillary muscles, resulting in fusion and shortening of these supporting structures (5). Variations in the magnitude and location of these changes account for the entire spectrum of mitral valve pathology, ranging from minor involvement to significant stenosis and/or insufficiency.

Lesions of the mitral leaflets may involve the valvular edges alone, may extend to include the valve proper, or may involve the chordae tendineae and papillary muscles as well. Involvement of the minor (posterolateral) valve leaflet usually is more extensive than that of major (aortic) leaflet. Thus, while the minor leaflet may show marked thickening and be firmly fixed by shortened chordae tendineae, the major leaflet may exhibit only minimal changes and retain wide mobility (6). Under such circumstances hemodynamically significant insufficiency is less apt to be present.

Harken and his colleagues have classified mitral valvular changes into the two following major types:

The Diaphragm Type

In this the major cusp proper is still soft and elastic, or only slightly thickened, and remains mobile. Three subtypes may be encountered:

A. Simple adhesions along the thickened fibrotic edges with fusion of the cusps primarily at the commissures so that a shortened and narrowed slit results, the valve proper remaining in a relatively undistorted state. No insufficiency can be detected. Commissurotomy can be performed in this type of valve with ease, and with maximum restoration of valvular function.

B. Thickening of the cusps proper in addition to adhesions along the valve edges. In this type the mobility of the minor cusp is somewhat impaired, the major cusp remaining mobile. The chordae tendineae are only minimally involved. If insufficiency coexists, it is only minimal.

C. Diaphragmatic funnel subtype. The minor cusp and its chordae, as a result of fibrosis and scarring are more or less fixed and rigid. However, the major cusp is only slightly thickened near the edge and, with its chordae essentially normal, is still able to maintain an adequate range of motion; thus the competency of the outflow tract of the left ventricle is maintained. The valve is retracted towards

the left ventricular cavity, involving primarily the posterolateral cusp (which does not constitute part of the outflow tract) and appears somewhat like a funnel. Mitral insufficiency is usually not pronounced because the anteromedial or major cusp remains essentially intact.

The Funnel Type

Both the major and minor cusps are fibrotic and thickened, with resultant complete loss of mobility. Extensive fusion of the chordae and scarring of the papillary muscles are present, and may even form a secondary stenotic opening. The fused cusps assume the form of a rigid funnel which does not close effectively, allowing reflux of appreciable amounts of blood into the left atrium during ventricular systole. The anteromedial cusp, being deformed and rigid, no longer effectively separates the mitral orifice from the aortic outflow tract and stenosis is almost always subsidiary to insufficiency. Commissurotomy offers little for correction of this type of valve.

THE HEMODYNAMIC CHANGES OF MITRAL STENOSIS

When the mitral valve area approaches 1.0 cm² in the course of its contraction, there is an elevation of the left atrial pressure from a normal of 5 to 10 mm Hg to as high as 20 to 25 mm Hg in severe cases. This results in a diastolic atrioventricular filling gradient across the valve, with hypertrophy and dilatation of the left atrium. In the majority of cases, consequent to the elevation of left atrial pressure, progressive pulmonary hypertension, initially passive, develops, with progressive diminution in the caliber of the lumina of the pulmonary arterioles (5, 7-11). In accordance with Poiseuille's Law (which, to be sure, is only approximately applicable to blood flow in the smaller caliber non-rigid pulmonary vessels) the ensuing small change in the radius and capacity of these vessels produce marked changes in the resistance to flow (8). As the pulmonary vascular resistance increases, assuming a relatively constant pulmonary blood flow, the pressure within the pulmonary circulation rises (pressure = resistance \times flow) (7, 8, 10). Apparently, pulmonary vascular resistance does not increase until the mitral valve has reached this critical size. Thereafter, the resistance is roughly proportional to the size of the orifice. This assumption is supported by the finding that after mitral commissurotomy, regression in pulmonary vascular resistance often occurs (9, 10, 12).

There is another group of patients who develop marked pulmonary vascular resistance and pulmonary hypertension early in the course of their disease. The rapid development of pulmonary vascular resistance in these patients reduces pulmonary blood flow, aborting the development of left atrial and pulmonary capillary hypertension. In this group, pulmonary congestive symptoms are transient. Wood (13) reported that only 20 per cent of patients with severe pulmonary hypertension ever developed prominent pulmonary congestive symptoms; in the other 80 per cent the clinical picture of right ventricular failure predominated almost from the start.

The normal pulmonary circulation is a low pressure system, with mean pressures of approximately 15 to 20 mm Hg. In severe mitral stenosis the mean pulmonary artery pressure may rise to as high as 70 to 80 mm Hg or more. The ma-

jority of patients, however, have mean pulmonary artery pressures of 35 to 40 mm Hg, with a further elevation on exercise. In addition to the effect of the prolonged pulmonary hypertension on the pulmonary vessels, changes in the lung parenchyma also occur, characterized by perivascular inflammation, resulting in pulmonary fibrosis and diminished compliance of the lungs. Alveolo-capillary exchange of gas is impaired and the over-all pulmonary functional reserve is reduced (37).

Pulmonary vascular resistance is attributable to at least two factors: the structural changes in the pulmonary vasculature, and/the vasoconstrictive influences on the pulmonary vessels; this vasospastic element is ascribed to the passive pulmonary hypertension, and possibly to varying degrees of hypoxia (14).

The relative importance of each of these two factors remains conjectural (8, 13, 15, 16). In favor of the occurrence of significant pulmonary vasoconstriction is the reduction of pulmonary vascular resistance by the administration of ganglionic-blocking agents or acetylcholine (14, 17). When acetylcholine is injected into the pulmonary artery (where its action is short-lived and is dissipated before reaching the systemic circulation) it will produce a striking fall in pulmonary artery pressure without a reduction in cardiac output in many patients with mitral stenosis and pulmonary hypertension (18). In addition, one often observes a profound fall in pulmonary hypertension following immediately after adequate surgical correction of the stenotic valve. Obviously, were the pulmonary vascular resistance in these particular cases due primarily to structural changes in the vessels, this reduction could not be expected to occur so promptly.

On the other hand, progressive structural changes certainly do occur in the pulmonary arterioles. There is initial hypertrophy of the media, followed by intimal proliferation with diminution of the lumen of the vessel. In the more advanced cases one also finds generalized fibrotic and thrombotic lesions in the vessels, at times with complete occlusion of many of them. Arteriosclerotic changes also occur as a late manifestation (3, 15, 16, 19, 20). In many advanced cases pulmonary vascular resistance and pulmonary hypertension subside only very gradually over a period of several years subsequent to commissurotomy, suggesting that these structural changes also are functionally significant (21).

Cardiac output in symptomatic mitral stenosis is usually diminished, at least with exercise. This is a result of obstruction to the inflow of blood into the left ventricle by the stenotic valve and to the resistance offered to flow through the pulmonary vascular bed. Consequent to the pulmonary hypertension, right ventricular hypertrophy and dilatation progressing to right ventricular failure eventually occurs with right atrial enlargement and venous hypertension as the end stage (5, 9-11, 22).

THE DIAGNOSIS OF MITRAL STENOSIS

The symptomatic phase of mitral stenosis is ushered in by manifestations of left atrial failure and pulmonary congestion, such as exertional dyspnea, nocturnal dyspnea, orthopnea and hemoptysis. Initially symptoms may be provoked only after severe exertion or excitement, but they soon become incorporated into the patients' daily living. As the disease progresses to the stage of increased pul-

monary vascular resistance with pulmonary hypertension, these symptoms are gradually replaced by those of right ventricular failure. Fatigue, abdominal discomfort due to enlargement of the liver, and peripheral edema become prominent. Palpitations occurring at any stage of the disease, may herald the onset of atrial fibrillation, at first paroxysmal, later fixed. Peripheral and cerebral embolization secondary to atrial fibrillation and left atrial enlargement may occur. Pulmonary embolization and infarction may also complicate the picture.

The classical rumbling apical diastolic murmur with presystolic accentuation occasionally may be greatly diminished or indeed inaudible even in the presence of severe stenosis (47), notably when atrial fibrillation modifies the intensity and quality of the murmur because of ineffective atrial contraction. In "pure" mitral stenosis the first heart sound is accentuated and this is a reliable guide to the absence of significant mitral regurgitation. The presence of an opening "snap" of the mitral valve is the most constant and frequent physical sign of uncomplicated mitral stenosis. It has been shown that the accentuated first heart sound and the opening "snap" reflect a high degree of mobility and elasticity of the major cusp, and therefore the likelihood that mitral surgery will be effective (23). On the other hand, absence or diminution of the opening snap is often noted in conjunction with severe valvular calcification and usually accompanies predominant regurgitation (24). Elevation of the pulmonary artery pressure is often suggested by the presence of an accentuated and split pulmonic second sound. If right ventricular hypertrophy is marked one may detect a diffuse substernal "lift."

The electrocardiogram in uncomplicated mitral stenosis may give evidence only of left atrial enlargement characterized by broad, notched P waves ("P mitrale"). Wood suggests that the "P mitrale" should be present in all cases of mitral stenosis (with regular sinus rhythm) severe enough to warrant surgery. The pattern of right ventricular hypertrophy, represented by right deviation of the electrical axis, and tall delayed R waves in the right precordial leads and in aVr suggest predominant mitral stenosis complicated by pulmonary hypertension.

Radiographic and fluoroscopic examination in mitral stenosis reveals an enlarged left atrium, best demonstrated by deviation posteriorly and to the right of the barium-filled esophagus. It is also evident in the postero-anterior projection by the presence of a shadow superimposed on the right side of the cardiac silhouette ("double density"). Right ventricular hypertrophy is suggested by encroachment on the retrosternal space by the enlarged chamber, especially in the right anterior oblique projection. In the postero-anterior view the apex appears rounded and elevated. The pulmonary artery segment is prominent, and the tip of an enlarged left atrial appendage may be seen. It is often difficult to be certain to what degree right and left ventricular enlargement contribute to the cardiac silhouette seen in advanced mitral disease. Calcification of the mitral valve may be detected, and if pronounced, generally indicates a serious degree of mitral regurgitation.

Catheterization of the right heart and pulmonary vessels allows direct determination of right atrial, right ventricular and pulmonary artery pressures; wedging the catheter into a peripheral branch of the pulmonary artery measures the

"pulmonary capillary" pressure. This measurement provides an indirect estimate of left atrial pressure since a closed manometric system communicating with the left atrium is thereby established. Normal pressures are approximately 0-5 mm Hg in the right atrium (mean pressure), 25/0 mm Hg in the right ventricle, 25/8 mm Hg in the pulmonary artery (mean pressure 15 to 20 mm Hg), and 5 to 8 mm Hg as the "pulmonary wedge" pressure. The earliest hemodynamic changes in mitral stenosis are reflected by an increased "pulmonary capillary" pressure. With progression of the disease, as the "pulmonary capillary" (and left atrial) pressures approach 25 to 30 mm Hg, elevation of the pulmonary artery pressure begins to appear, initially on exercise alone, and then at rest. In moderately advanced disease mean pulmonary pressures of 40 to 50 mm Hg are not uncommon, with a further rise on exercise. In more advanced cases mean pulmonary artery pressures as high as 80 to 90 mm Hg may be recorded (8). A proportionate rise in right ventricular systolic pressure is noted and, with the advent of right ventricular failure, elevation of the right ventricular end-diastolic pressure appears.

With the development of techniques to catheterize the left cardiac chambers, this more direct approach to the hemodynamic alterations of mitral stenosis is usually resorted to when cardiac catheterization is indicated. Either transbronchial or a percutaneous approach through the back may be utilized to introduce the catheter directly into the left atrium without undue risk. By simultaneous pressure recordings in the left atrium and left ventricle, an estimate of the diastolic filling gradient across the mitral valve may be obtained. Normally there is no gradient across the valve. Narrowing of the valve orifice constitutes an obstruction in the face of which diastolic blood flow can be effectively maintained only by a rise in left atrial pressure to produce a significant pressure gradient (5 mm Hg or greater) across the compromised mitral valve. The presence of such a gradient is *prima facie* evidence of significant mitral stenosis (30). Recent investigation has demonstrated that in early mitral stenosis the A-V filling gradient may be inconspicuous at rest, but becomes apparent with exercise. It should be emphasized that in the majority of patients the diagnosis of mitral stenosis of a degree severe enough to warrant surgery can be established without resorting to cardiac catheterization. In selected cases, however, when the clinical picture is obscure, when other diagnostic procedures are inconclusive, or when the symptoms are disproportionate to the objective findings, cardiac catheterization, especially of the left side of the heart, is essential to determine the presence and degree of stenosis.

INDICATIONS FOR MITRAL COMMISSUROTOMY

Once the diagnosis of mitral valvular disease with significant stenosis has been established, the advisability of surgical intervention must be determined. In the light of present day knowledge patients who are completely asymptomatic, *i.e.* Class 1 of the American Heart Association classification,* are not considered

* Class 1. Cardiac disease, but no limitation of physical activity.

Class 2. Slight limitation of physical activity.

Class 3. Marked limitation of physical activity; symptoms even with the milder forms of activity.

Class 4. Discomfort with any physical activity; may even be present at rest.

suitable for surgery by most investigators (25-31). It is interesting to note, however, that Bailey has recently operated on patients in Class 1 who chose to undergo surgery because of concern about future progression of their disease, and noted valve openings as small as 1.5 cm² or less, emphasizing the compensatory capacity of the heart (5).

The prime indication for commissurotomy at the present time is evidence of progression of the disease. The early Class 2 patient with mild, non-progressive symptomatology may be considered on an elective basis. Frequently, with simple medical measures and a minor readjustment of the patients' activities, these patients enjoy a rather satisfactory state of compensation, and a relatively active life barring such hazards as embolization. However, the striking decrease in operative mortality and morbidity in this group of patients over the past 10 years (from 14% to 1%) and the excellent operative results obtained, combined with the disability which may be imposed under medical management even at this stage of the disease are cogent arguments for early consideration of surgical intervention (32).

Patients in late Class 2 or in Class 3 constitute the larger number of surgical patients. Once the disease has progressed to this stage it carries the implication of shortened life expectancy and increased morbidity. Levine has noted that the average period between the onset of signs of congestive failure and death is four and three-fifths years. Grant (33) reported that 45 per cent of Class 3 subjects were dead at the end of a 10 year follow-up period. Olsen (34) found that only 51 per cent of 176 Class 2 (fibrillating) and Class 3 patients treated medically were still alive after seven years. In contrast, Harkens (35) reported that 87 per cent of 1000 similar patients treated surgically survived for seven years, even when the operative mortality of three per cent was included. Baily (5) (1000 cases) and Digliotti (6) (2000 cases) report similar results.

Patients in Class 4 are cardiac invalids. In the pre-surgical era they were doomed to a life of complete inactivity and early demise even with the best available medical therapy. The difference between the survival rates of surgically and medically treated Class 4 patients is striking. For example, in Olesen's group of medically treated patients, only six per cent were alive at the end of six years, while in Harken's group of operated patients, the survival rate was 54 per cent at the end of seven years, including an operative mortality of 24 per cent (35). The grave prognostic implication of Class 4 is further attested by the report that only 40 per cent of Class 4 medically treated patients are still alive after one year (37). It is noteworthy that although the operative mortality in Classes 2 and 3 has continued to fall with improved techniques and experience, the operative mortality in Class 4 patients has remained essentially unchanged at 20 to 25 per cent (5, 35). However, if the Class 4 patient survives an adequate commissurotomy, satisfactory and sometimes striking improvement is experienced. In fact, most larger series report approximately 80 per cent of patients improved after commissurotomy in Class 2 and 3, and 60 per cent improved in Class 4 (5, 28, 32, 35, 36). In view of this experience it is apparent that surgery should be performed before life is threatened and when much can be accomplished at a low operative risk. Once the patient has advanced into class 4 the operative risk becomes sig-

nificantly increased and the potentialities for rehabilitation are greatly diminished.

The onset of atrial fibrillation is considered by most investigators to be an indication for mitral commissurotomy (5, 28, 30, 32). By reflecting hypertrophy and dilatation of the left atrium due to atrial hypertension, this arrhythmia connotes moderately advanced mitral stenosis. In addition to the effect of atrial fibrillation in reducing cardiac output, it carries the added hazard of embolization which may be crippling or fatal.

Embolization is considered an important indication for mitral surgery. Although the use of anticoagulant drugs may provide some degree of protection against embolization, no completely satisfactory medical preventive measure is available. The incidence of preoperative embolization in mitral stenosis is 15 to 25 per cent in reported series (5, 28). If the patient is experiencing showers of peripheral emboli commissurotomy may have to be performed as an emergency procedure. Generally, operation is deferred for one or two months after major embolization, maintaining the patient on anticoagulants in the interim. Thrombi are reportedly found in the atrium and appendage in only half of cases after recent embolization. In fact Baronofsky states that thrombi are rarely found in the atrium of patients who have previously sustained embolization (38). Commissurotomy reduces the incidence of subsequent embolization (to less than 2%) by reducing stasis in the left atrium by effectively enlarging the mitral orifice, and by auricular appendectomy, thereby removing a nidus for stagnation of blood and thrombus formation.

Hemoptysis associated with mitral stenosis often is an indication for surgical intervention. Rust colored sputum indicates engorgement of the alveoli with red blood cells due to congestion of the pulmonary vasculature. Frankly, bloody sputum is generally caused by the rupture of engorged bronchial veins and occasionally, if very profuse, may be an immediate threat to life, necessitating emergency commissurotomy. Hemoptysis subsequent to valvuloplasty is almost non-existent.

Pregnant patients with mitral stenosis rarely require commissurotomy during the pregnant state. If the symptoms are mild, pregnancy can be well tolerated if carefully managed. On the other hand, Class 3 and 4 patients who first come under observation during the first trimester of pregnancy can undergo commissurotomy with little more risk than in the non-pregnant state. The alternatives to immediate operation are either interruption of pregnancy and then commissurotomy, or continuation of the pregnancy under careful medical management with subsequent commissurotomy. If commissurotomy is elected, it should be performed during the first trimester, since the operative risk is substantially increased later in pregnancy (5, 28).

RELATIVE CONTRAINDICATIONS TO MITRAL COMMISSUROTOMY

Associated Valvular Lesions

Mitral insufficiency. The discussion heretofore has been concerned primarily with the so-called essentially "pure" mitral stenosis; in practice, however, one encounters a spectrum of mitral disease, ranging from "pure" stenosis through

slight insufficiency to gross mitral regurgitation. McDonald (12) noted a distinct relationship between the mitral valve area and the predominant lesion in patients with pronounced symptoms. Three grades of valve area were investigated: less than 0.8 cm², 0.9 to 1.6 cm², and 1.7 cm² or larger. The smallest areas corresponded to "pure stenosis," the intermediate sizes to "mixed" lesions, and the larger valve areas to predominant mitral regurgitation. Although mitral stenosis and insufficiency may coexist, and the physical findings of both may be present, in selecting patients for commissurotomy one must determine the predominant lesion. With the development of effective techniques for the repair of regurgitant as well as stenotic valves, particularly with the aid of extracorporeal circulation, all mitral lesions will be amenable to surgery.

The differentiation of predominant mitral stenosis from insufficiency cannot be made on the basis of symptomatology. Most patients with gross mitral regurgitation demonstrate an apical holosystolic blowing murmur transmitted into the axilla. The absence of this murmur virtually excludes significant mitral incompetence. Between these two extremes, one cannot correlate the degree of insufficiency with the intensity of the murmur. The absence of an "opening snap" of the mitral valve and/or a normal or diminished first heart sound rather than an accentuated one also suggests predominant insufficiency (12, 16). Left ventricular hypertrophy (in the absence of aortic valve disease), demonstrated either by displacement of the apex impulse outward and downward or by radiographic or electrocardiographic evidence, is compatible with predominant mitral regurgitation, and excludes significant mitral stenosis. The finding of neither a left nor a right ventricular hypertrophy pattern on electrocardiogram should also make one suspicious of significant mitral regurgitation. Left heart cardiac catheterization may detect the presence of insufficiency by demonstrating a regurgitant or "V" wave in the left atrial pressure tracing, but this is an inconstant finding (6). Many other procedures have been suggested to delineate the predominant lesion but, as yet, there is no absolute clinical or laboratory method. Occasionally one must resort to exploratory thoracotomy to make the correct diagnosis; the relative safety of the procedure makes this feasible.

Aortic regurgitation. If this lesion is prominent, mitral commissurotomy utilizing a closed heart technique should not be performed (23, 28). If minor in degree, as judged by a normal or near-normal diastolic pressure, and the absence of the other hemodynamic signs of free regurgitation (Corrigan's pulse, Duroziez's sign, etc.), this lesion is in itself not an absolute contraindication to the conventional mitral commissurotomy. Some believe, however, that patients with even minor degrees of aortic insufficiency may become worse after mitral commissurotomy due to the increased blood flow into the left ventricle which the incompetent aortic valve cannot handle. With the advent of open heart surgery, however, both valvular lesions can be dealt with concomitantly. One often notes a diastolic blowing murmur along the left sternal border in mitral stenosis (Graham-Steell murmur), associated with pulmonary hypertension and relative pulmonic insufficiency, which should not be confused with the murmur of aortic insufficiency. The Graham-Steell murmur generally disappears after successful commissurotomy.

Aortic stenosis associated with mitral stenosis is not a contraindication to commissurotomy provided the aortic valve is attacked concurrently. If the aortic stenosis is not relieved, commissurotomy, by increasing the influx of blood into the left ventricle, places an added burden upon an already compromised left ventricle (28, 39, 40).

Tricuspid valve lesions are rare. Significant tricuspid stenosis, if present, can be attacked by a right-sided approach as described by Bailey (5), at the same time the mitral valve is opened. Tricuspid insufficiency is generally relative, consequent to the right ventricular enlargement occurring in advanced mitral disease. It often improves after successful mitral valve correction and reduction in the pulmonary hypertension.

Acute Rheumatic Fever

The diagnosis of active rheumatic carditis is difficult in these patients, since the classical Jones' criteria are difficult to apply (28). If rheumatic activity is suggested by changing murmurs, pericarditis, associated polyarthritis, or by unexplained fever associated with acute phase reactants and elevation of the antistreptolysin titer, commissurotomy is best postponed. Active carditis makes the surgery more hazardous, and increases the possibility of later re-stenosis of the valve (41). If the patient exhibits only minor, non-specific abnormalities, such as unexplained low grade fever, elevated ESR or C-reactive protein, etc., these should not be construed as necessarily representing rheumatic activity. If a clear indication for commissurotomy is otherwise present, one may proceed with surgery. It should also be mentioned that there appears to be no correlation between the incidence of Aschoff bodies in the auricular biopsies and the clinical course of these patients.

Subacute Bacterial Endocarditis

This is an absolute contraindication to mitral commissurotomy. After a waiting period of three to six months after successful treatment and reevaluation for the appearance of involvement of other valves, surgery may be performed.

Age

Advancing age is not a contraindication to commissurotomy *per se*. In fact, when similar stages of the disease are compared, the operative risk and percentage of improvement are identical in younger and older age groups (42). However, one must consider the possibility of associated coronary artery disease and other degenerative diseases in the older age groups, and weigh the expected benefit from successful surgery against the life expectancy of the patient treated conservatively.

MITRAL COMMISSUROTOMY AND ITS COMPLICATIONS

There is general agreement as to the advisability of finger fracture of the valve before any attempt is made with the knife (2, 25, 26, 35, 43-47). The separation of the commissures by digital pressure alone is indicated whenever stenosis is due

chiefly to a fibrotic fusion of the commissures. The best surgical results are obtained where the leaflets are still elastic and do not show sclerosis or calcification. Digital splitting, however, may be completely satisfactory even in the presence of sclerotic and calcified valvular structures if these changes are limited to the surface of the leaflets without involving the commissures, and if only relatively soft tissue keeps the cusps adherent (25, 36, 44, 47-49). Dogliotti (36) reported a series of 2000 cases of mitral commissurotomy in which splitting alone was employed in 67 per cent of these cases.

In most cases the splitting maneuver is performed primarily on the anterior commissure since it is more accessible; however, pressure should be directed toward that commissure which at the exploration seems easier to split. The valvular separation should be carried out gradually so that the earliest indication of any created regurgitation may be recognized and further manipulations of that commissure terminated at once, limiting to an insignificant amount any incompetence which might inadvertently be produced (36, 43). Those patients in whom a mild degree of insufficiency is unavoidably produced at surgery do almost as well as those without any insufficiency; however, those with more pronounced operative regurgitation have proportionately poorer results (13, 16, 26, 36, 48, 49). In many instances one commissure may be sclerotic or deeply calcified while the other, although fused, may still be elastic and yield easily to the finger. In these cases the complete separation of the softer commissure can produce an opening of 3 to 3.5 cm². Under such circumstances this must be considered an adequate opening of the mitral valve (36).

Instrumental commissurotomy is appropriate in cases in which digital pressure is not effective or the enlargement so obtained is considered to be inadequate. When such a situation exists further finger manipulation can be very dangerous because any of the following may occur: a. laceration of the auricular appendage or perforation of the ventricular myocardium with hemorrhage, b. prolonged occlusion of the atrioventricular orifice leading to diminished cardiac output, hypotension, cardiac arrhythmias, or asystole, c. mobilization of atrial thrombi, d. laceration of the valve leaflets resulting in mitral regurgitation. For maximum restoration of cusp mobility both instrumental commissurotomy and finger fracture should attempt to extend the incision in the commissure up to the fibrous mitral ring (2, 36, 43, 44, 47, 48, 51). When the commissures are distorted and ill-defined it is best to err on the side of cutting toward the posterior leaflet and its chordae rather than toward the anterior leaflet. The rationale for such a maneuver is twofold. First, since the posterolateral cusp does not usually constitute part of the aortic outflow tract, an incision into this cusp does not produce the degree of hemodynamically significant regurgitation that would obtain if a similar cut were made into the anteromedial cusp. Second, if the anterior leaflet should be cut a wide split in the cusp is effected by the pulling action of the papillary muscles and their chordae, thus separating the cusp at the site of the incision and only aggravating the incompetence of the valve. This does not occur if the posterolateral leaflet is cut, because of its chordal distribution as described under the normal anatomy (42, 50).

At times one may only be able to initiate fracture with the finger and an instrument may be necessary for completion of the incision; the converse of this also occurs (36, 44, 48, 49).

It has been amply demonstrated that the best functional results are obtained in those subjects in whom the greatest enlargement is obtained. Therefore, every attempt should be made to enlarge the orifice to as near normal size as possible (43, 44, 50-52). In a well-performed commissurotomy Dogliotti (36) noted that the initial size of the orifice bore no relation to how great an enlargement was obtainable. Despite a great increase in size of the orifice, there is usually no increase in the incidence of surgically induced insufficiency. Operation is considered satisfactory if the surface area of the orifice can be enlarged to 3 to 3.5 cm², but lesser enlargement of the mitral ring must be considered adequate if, because of the local conditions, further manipulation might be dangerous. Such a situation exists if thrombi are present in the left atrium or if verrucae or particles of calcium palpated on the valve cusps or near the commissures could be easily dislodged by repeated maneuvers (5, 36, 44, 45). In some cases the surgeon may encounter anatomic situations in which all attempts at commissurotomy will fail, and produce either mitral insufficiency or accentuate a pre-existing insufficiency. This situation exists particularly when the valvular leaflets are retracted and have completely lost their original shape, due to marked valvular calcification, and to papillary muscles forming a musculofibrous canal, *i.e.*, the "funnel-type" stenosis previously described (1, 36, 49).

Re-stenosis of the valve probably occurs only if the valve is not adequately opened, since if the fused commissures are split or cut all the way to the annulus there is rarely a recurrence of stenosis. By completely splitting the fused commissure to the annulus not only is a larger mitral orifice obtained, but in effect a valvuloplasty is performed since this maneuver increases the mobility of the cusps and thus improves valvular function (5, 35, 39, 44, 50, 51). The effectiveness of the valve fracture may be further evaluated by comparing direct pressure measurements of the pulmonary artery, left atrium, and the atrioventricular gradient across the mitral valve before and after commissurotomy. If a significant gradient persists (greater than 5 mm Hg) a more adequate commissurotomy is necessary, if feasible. Pulmonary hypertension, if present, is usually significantly reduced except when there are pronounced organic vascular changes.

In Dogliotti's series of 2000 reported cases the mortality was lowest in patients with elastic valves (2.5 per cent), slightly higher in those who presented with sclerotic valves (2.8 per cent), and appreciably higher in those patients having extensively calcified valves (5.6 per cent). The mortality appeared to be related more to the anatomic condition of the stenotic valve than to the operative technique employed (36).

There are certain obvious limitations to the orthodox left-sided approach to the mitral valve. This, in conjunction with the relative frequency of multivalvular involvement, has prompted Bailey to introduce a right thoracotomy technique when indicated. Through this right-sided approach the heart is exposed and an incision is made into the interatrial groove within a pursestring suture.

The left atrium is entered with the exploring finger through an opening produced in the interatrial septum. It is his belief that there are certain distinct advantages to this approach. The most important of these is the ready accessibility to the tricuspid and aortic valves for simultaneous corrective surgery. A second advantage is the much greater facility and accuracy with which the posterior mitral commissure can be separated, either digitally or instrumentally. Bailey estimates that an expert operator usually can achieve an approximately 50 per cent larger opening of the mitral valve by this technique without any increase in the production of regurgitation. This approach accordingly is advocated by Bailey for secondary commissurotomy since it has the additional advantage that the left atrial cavity can be entered through the virginal right pleural cavity. A third advantage is that it obviates the use of the left auricular appendage as an entrance passageway. Since this appendage has been found to contain thrombi in about 30 per cent of all patients operated on for mitral stenosis it would seem that by the very act of inserting a finger into its lumen the operator must incur an unavoidable risk of dislodging thrombotic material. The right-sided route would seem to minimize this risk since the operating finger approaches the mitral valve from the right through an incision which is made through the septal wall of the left atrium (5, 53).

Hypotension may occur at any time during the course of the procedure. Excessive blood loss during the intra-cardiac maneuvers (including laceration or perforation of the myocardium), occlusion of the mitral orifice for a protracted period of time, and cardiac arrhythmias (especially rapid atrial fibrillation) are the etiologic factors usually incriminated. Shock may be encountered even before the initial skin incision. Positioning of the patient on his right side may significantly shift the mediastinum and be responsible for mechanically reducing the cardiac output. The relaxation associated with general anesthesia dilates the peripheral vascular bed. When occurring in patients with a reduced and often fixed cardiac output, as in advanced mitral stenosis, a precipitous and alarming loss of effective circulation may be the consequence. Vasopressor drugs and/or blood transfusion may be required to maintain the blood pressure.

Irreversible cardiac arrest is an ever present possibility, especially in far advanced cases (54). Today, such patients can be operated on with the aid of extracorporeal circulation to insure adequate coronary perfusion during the procedure.

Embolization may occur at any time, but is more likely to occur during manipulation of the auricle or the mitral valve, often in spite of temporary intra-thoracic occlusion of the supra-aortic atrial trunks. It has been reported in up to 10 per cent of cases with preoperative embolization. Emboli may originate from the auricular appendage, the left atrial wall or from calcifications around the mitral orifice. Embolization is usually to the central nervous system and may be fatal (4). Embolization in the immediate postoperative period is a less likely occurrence (32, 35). Usually the patient is sufficiently awake at the end of the operation to move his extremities on command, enabling one to detect operative embolization.

Cardiac irregularities occurring postoperatively require careful regulation. Auricular fibrillation occurs in a substantial number (15-20%) of postoperative

patients in whom normal sinus rhythm was present postoperatively (5, 13, 32, 35). The majority of those who do fibrillate revert spontaneously, and most of the remainder do so under therapy; a few remain with permanent atrial fibrillation. Wood (13) states that conversion should not be attempted before the end of the second week, due to an initial refractory phase.

Congestive heart failure secondary to rapid auricular fibrillation or mitral insufficiency (pre-existing or surgically produced) is another postoperative complication. It occurs not infrequently in advanced cases, often in association with pulmonary embolization. Less advanced cases often present no postoperative problems.

The "post-commissurotomy syndrome," consisting of malaise, fever, leukocytosis, elevated sedimentation rate and C-reactive protein, electrocardiographic evidence of pericarditis with or without pericardial or pleural effusions and pleuritic chest pains, may occur in from 10 to 25 per cent of patients. This syndrome, usually appearing between the second and twelfth week after operation, may recur for many months and occasionally for years, but nevertheless has a good prognosis. Treatment consists of administration of salicylates and/or corticosteroids. The appearance of the syndrome seems not to affect the ultimate benefit obtained from commissurotomy (23, 55, 56).

Other less frequent postoperative complications are hemopericardium with tamponade and postoperative depressive or confusional psychotic states; the latter are always temporary.

ANALYSIS OF RESULTS OF MITRAL COMMISSUROTOMY

Between April 1957 and October 1958, 42 patients underwent surgery for mitral stenosis at The Mount Sinai Hospital. All of the operations were either performed or supervised by a single surgeon*. Current follow-up data are available on every patient, with follow-up periods ranging from six to 18 months. The patients have been classified according to the American Heart Association functional classification, which has already been referred to.

It should be mentioned at the outset that exaggeration on the part of the patient concerning an increase in functional capacity after commissurotomy, and on the other hand, anxiety or self-imposed restrictions with reluctance to attempt increased activity after operation must be carefully assessed before deciding the extent to which the patient actually benefited from the operation. Many patients first realize the magnitude of their preoperative disability only by comparison with the dramatic relief of symptoms following surgery (16, 32, 35).

Preoperatively, there were 20 patients in Class 2, 20 patients in Class 3, and 2 patients in Class 4. The ages varied from 15 to 56 years. The results of surgery were arbitrarily classified as follows:

Excellent: A patient converted to Class 1, or with only minimal symptomatology.

Fair: A patient with definite but not striking improvement, who is classified at least one class better than preoperatively.

* Ivan D. Baronofsky, M.D.

Unimproved: A patient whose symptoms have been unaltered consequent to surgery.

Worse: A patient whose symptoms have worsened following surgery.

Deaths: These include operative, early postoperative, and late demise (subsequent to discharge).

In 29 patients pure stenosis was found at surgery and in 13 patients there were varying degrees of associated mitral regurgitation.

The overall number of patients considered to be significantly improved was 30 (71 %). Of these in 25 (60 %) the results were considered excellent, five were classified as fair. Two patients were unimproved, three were worse subsequent to commissurotomy, and three late deaths occurred subsequent to discharge.

Further analysis of these figures according to functional Class reveals that 16 of the 20 patients (80 %) classified preoperatively as Class 2 were considered to be improved. Of these 13 had an excellent result and three a fair result. Two were considered to be unimproved, one patient was worse subsequent to surgery, and there was one late death, possibly due to embolization.

Of the 20 Class 3 patients, 14 (70 %) were improved, of whom 12 had an excellent result and two a fair result. Two patients were apparently worse after commissurotomy and there was one late death. There were three hospital deaths in this group, two of which were operative. Two of these were secondary operations for mitral stenosis and will be discussed later.

There were only two patients classified as Class 4. One died while in the hospital, the other one year postoperatively.

The postoperative objective criteria of mitral stenosis, such as the electrocardiogram and cardiac size determined roentgenographically, have shown little change in spite of obvious clinical improvement. However, if significant mitral regurgitation had been produced, these modalities would clearly reflect the change.

The auscultatory findings also correlate poorly with the degree of subjective benefit. The rumbling apical diastolic murmur continues to be heard, although with markedly diminished intensity, in the majority of patients after a successful commissurotomy. This murmur may persist postoperatively with only a trivial degree of stenosis. The accentuated apical first heart sound is usually present even with mild degrees of stenosis; consequently its return to normal in only a relatively small percentage of postoperative patients (approximately 25 %) is not unexpected. Loss of the opening "snap" also occurs in only about one-third of patients; about half of these have an excellent clinical result and the remainder have developed surgically-induced mitral insufficiency (16, 24). A Grade 1 or 2 pre- or postoperative apical blowing systolic murmur is usually compatible with a good clinical result, but if greater intensity a significant degree of mitral insufficiency may be assumed to have developed (16).

There follow brief abstracts of those patients who were not improved as a result of surgery, and of both the early and late deaths. It will be noted that these patients presented one or more of the following factors which have been considered to reduce the chance of operative success: marked cardiac enlargement, sig-

nificant mitral insufficiency, a markedly calcified mitral valve, prolonged congestive heart failure, atrial fibrillation, or marked pulmonary hypertension (16, 57).

CASE REPORTS

Unimproved

Case #1. M. G., a 33 year old female in progressive Class 3, was noted at operation to have a finger tip (0.5 cm^2) valve opening with a gradient of 21 mm Hg across the valve. Both commissures were split, establishing an opening of 2.5 to 3.0 cm^2 with a consequent reduction of the gradient to 10 mm Hg; there was no regurgitation. Postoperatively the patient did very well for the next eight months and then began slowly to regress until presently, 11 months after commissurotomy, her activities are rather limited and her overall condition unimproved compared with her preoperative status.

It may be mentioned that the patient has been maintained on Gantrisin[®] prophylaxis so that rheumatic carditis is probably not the responsible agent. Usually, if a patient sustains his initial improvement for greater than six months, the outlook for a successful valvulotomy is excellent. The residual gradient of 10 mm Hg in the light of the patient's course, appears to have been significant.

Case #2. M. W. was a 56 year old male, Class 2, whose symptoms consisted primarily of dyspnea after rather strenuous activity and occasional mild hemoptysis. At operation a 1 cm^2 valve orifice was enlarged to 3.5 cm^2 employing both the finger and the knife. A mild degree of insufficiency which existed preoperatively was unaltered by the commissurotomy. Although the patient can carry objects weighing 60 pounds or more, he feels there has been no improvement since surgery.

Worse

Case #1. T. K., a 29 year old female, Class 3, underwent commissurotomy, enlarging the mitral orifice to 4 cm^2 . The fusion at the anterolateral commissure required the valvulotome. Subsequent to cutting the commissure a moderate degree of regurgitation was noted, with a prominent "V" wave in the left atrial pressure tracing. Postoperatively the patient developed mild congestive heart failure but refused open heart surgery for correction of her mitral insufficiency.

Case #2. M. P., a 40 year old female, Class 3, was noted at operation to have a 1.5 cm^2 valve orifice. This was enlarged to 4 cm^2 , with abolition of the pre-commissurotomy gradient of 17 mm Hg. There was a "faint puff" of regurgitation. Postoperatively, there was only a soft presystolic murmur with an opening snap; there was no systolic murmur. The patient is now nine months postoperative and states that she can engage in fewer activities now than before operation. This patient is one in whom a good result would have been anticipated. It should be mentioned that she is markedly obese and has made no effort to reduce.

Case #3. A. S., a 39 year old female in progressive Class 2, was found to have a mild degree of regurgitation at operation. The valve orifice was opened to 3 cm with no reported increase in regurgitation. The patient is now 18 months postoperative and is reported to be more disabled than prior to surgery.

Early Mortality

Case #1. M. B., a 36 year old male, Class 4, with chronic congestive heart failure and ascites, was noted at operation to have a giant left atrium and a large left ventricle with both apical systolic and diastolic thrills. The right ventricular pressure was 68/7; the pulmonary artery pressure was unavailable. There was rather marked regurgitation and a diastolic gradient of 20 mm Hg across the mitral valve. The valve was markedly calcified, requiring cutting of the anterolateral commissure. This maneuver reduced the gradient to 13 mm Hg, but also aggravated the insufficiency somewhat, with an increase of the left atrial pressure from a mean of 36 before to a mean of 50 mm Hg after commissurotomy.

Postoperatively, the patient developed "hyposystolic shock" probably due to acute left ventricular failure secondary to the increased insufficiency, with oliguria, azotemia and eventually death eight days postoperatively. Post mortem examination disclosed significant mitral insufficiency and bi-ventricular enlargement.

Case #2. V. B., a Class 3, 38 year old female with auricular fibrillation, experienced pulmonary edema during right heart catheterization. The pulmonary artery pressure was 110/66 and the right ventricular pressure 94/6. At operation the patient was turned into the right lateral decubitus position, with a progressive drop in blood pressure which would not respond to neosynephrine. The heart was quickly exposed and noted to be beating feebly. A pin-point mitral opening was discovered and this was quickly split but to no avail. Post mortem examination revealed a tight mitral stenosis, marked right ventricular hypertrophy, arteriosclerosis of the pulmonary vessels, and severe mitral lung disease.

Case #3. D. E., a 43 year old, Class 3 female with multiple episodes of congestive heart failure, in 1955 underwent a thoracotomy for mitral commissurotomy, but the left atrium could not be entered due to a stenotic appendage. At a second thoracotomy the patient developed hypotension early in the procedure and the valve was quickly incised. Irreversible cardiac arrest ensued.

Case #4. A. M., a 30 year old female, underwent a valvulotomy in December 1951. Her symptoms gradually returned, classified as a far advanced class 3 at the time of surgery. At operation she was noted to have a 0.5 cm² fibrotic valve requiring the knife. The orifice was enlarged to 3.5 cm² with a consequent mild degree of regurgitation. On the fourth post-operative day the patient developed right pleuritic chest pain with hemoptysis. A presumptive diagnosis of pulmonary infarction was made and anticoagulation therapy instituted. On the sixth postoperative day she suddenly developed severe dyspnea, cyanosis and right chest pain. Shock ensued which was refractory to both Levophed[®] and blood transfusion. Post mortem examination revealed a satisfactory commissurotomy. There were no pulmonary emboli but 500 cc of blood was present in the left hemithorax, with some small areas of pulmonary infarction.

Late Mortality

Case #1. S. T., a 42 year old male, Class 4, with auricular fibrillation, had a mean left atrial pressure of 38 mm Hg and a right ventricular pressure of 73/7. The left atrial curve indicated some degree of insufficiency as evidenced by a prominent "V" or regurgitation wave. At operation a heavily calcified valve was enlarged from 0.5 cm² to 3.5 cm² with no reported increase in the regurgitation. The patient did well initially but three months postoperatively was readmitted with mild congestive heart failure. He was noted to have a Grade 3 blowing systolic murmur at the apex, radiating to the axilla. His electrocardiogram revealed a change from a preoperative right axis deviation to a postoperative left axis deviation and the chest films confirmed an increase in the size of the left ventricle; mitral insufficiency was apparently the responsible lesion. Subsequent to discharge he continued to have bouts of failure. He died suddenly 11 months after commissurotomy.

Case #2. H. T., was a 30 year old male, far advanced Class 3, with auricular fibrillation and multiple episodes of congestive heart failure. At operation the mitral valve would barely admit a finger tip (less than 0.5 cm²). There was a moderate degree of regurgitation. After commissurotomy the orifice was adequately enlarged to 3 cm² but with a marked increase in the insufficiency. Postoperatively, the congestive failure became more severe. The patient was rehospitalized 6 months after surgery, with right-sided chest pain, bilateral pleural effusion and marked congestive failure. His hospital course was complicated by influenza and multiple pulmonary infarcts. His condition slowly deteriorated and after a prolonged hospitalization he succumbed, approximately 10 months after his commissurotomy. Post mortem examination revealed a right lower lobe embolus with small old pulmonary infarcts, an enlarged right ventricle, left atrium and left ventricle, and a chorda tendineae that had apparently been cut at operation.

Case #3. L. N., was a 51 year old female, Class 2, with auricular fibrillation, who sustained a right hemiplegia and motor aphasia in June, 1958 consequent to a cerebral embolus. She was operated on one month later. A 3.5 cm² opening was obtained and there was no increase in a minimal pre-existing insufficiency. She did relatively well, except for the limitations imposed by her neurologic condition, until her death 1 year after operation, possibly due to another episode of cerebral embolization.

SUMMARY

- A. Mitral stenosis is discussed in both its medical and surgical aspects.
- B. The anatomy of the normal mitral valve is described emphasizing the role of the anteromedial or aortic cusp and its significance during mitral valve surgery.
- C. A description of the various types and degrees of mitral valve involvement is given.
- D. The diagnosis of mitral stenosis and methods of determining the degree to which it is hemodynamically significant are discussed.
- E. Current indications for and contraindications to mitral commissurotomy are summarized together with the operative and postoperative complications.
- F. An analysis of 42 cases operated on at The Mount Sinai Hospital is presented.

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Clinico-Pathological Conference

BLOODY ASCITES FOLLOWING RESECTION OF ILEUM

Edited by

FENTON SCHAFFNER, M.D.

A 53 year old white married insurance man was admitted to The Mount Sinai Hospital for the eighth time complaining of rapidly increasing abdominal swelling and weakness of ten days duration.

The first admission was nine months earlier at which time the patient stated he had cramps, mid-abdominal pain for about eight months and occasional diarrhea for two to three years. The abdominal pain came in attacks associated with diarrhea, distention, rumbling and gurgling and anorexia, and subsided in a few days. The diarrhea consisted of four to five watery movements per day. Two days prior to admission, another attack began but instead of diarrhea, vomiting occurred for the first time. He was admitted to another hospital where a nasogastric tube was passed and the patient given intravenous fluids. The vomiting stopped and diarrhea began. After two days the tube was removed and the patient transferred to this hospital. The patient had influenza in 1918, rheumatoid spondylitis in 1934 and had been on steroids for three to four months, given for the intestinal complaints.

On examination he was well nourished and well developed. His temperature was 100°F, pulse rate was 84 and regular, and blood pressure was 145/80. The only abnormalities were occasional inspiratory rhonchi over both bases of the lungs and moderate distention and tympany over the abdomen with tinkling bowel sounds. Some straightening of the spine was present.

Hemoglobin was 13.2 grams % and the white blood count was 6,700/cu mm with a normal differential count. Urinalysis was normal. Stool guaiac was 3+, BUN 8 mg %, serum sodium 143 mEq/l, potassium 3.7 mEq/l, CO₂ 31.8 mEq/l and chloride 103 mEq/l. C-reactive protein was 3+, Coombs test was negative as were several LE preparations, and bleeding time was 1'15", and clotting time 9'30". The remainder of the findings are presented in Table I.

Three days after admission the patient had a resection of 20 inches of terminal ileum. The cecum was transected just above the ileocecal valve and an end-to-end anastomosis was made. The patient made an uneventful recovery and was discharged on the 14th hospital day.

The patient was well for three months when he noted gradual increase in girth. After a month he became quite uncomfortable and he was admitted for paracentesis. On examination gross abdominal distention of the abdomen was seen with shifting dullness. No masses or organs were felt. Slight ankle edema was noted. Hemoglobin was 9.6 grams %. Ten liters of bloody ascitic fluid were removed and 20 mg nitrogen mustard was instilled into the abdomen. After two days the patient was sent home.

From the Department of Pathology, The Mount Sinai Hospital, New York, N.Y.

TABLE I
Laboratory Data

	1st Admission	2nd Admission	3rd Admission	5th Admission	7th Admission	8th Admission
Urine						
Sp. Gr.	1.006-1.020	1.001-1.006	1.014-1.007	1.007	1.004-1.010	—
Albumin	1-3+	0-3+	1-2+	1-2+	2-3+	—
RBC/HPF	2-packed	many	5-loaded	loaded	loaded	—
WBC/HPF	10-loaded	4-35	3-35	occasional	0	—
Casts	hyaline	granular	hyaline	granular	—	—
	granular	blood	granular	blood		
	pus		pus			
			blood			
Blood						
Hgb. (G %)	12.8-15.5	11.3-7.5	9.3-9.0	5.5-9.6	7.7-4.4	6.7-4.0
WBC (/mm ³)	8,000-10,250	9,600-7,100	7,850	10,350	7,300-22,600	14,500
Platelets (/mm ³)	420,000	306,000	—	—	300,000	—
ESR (mm/hr.)	36-43	65-80	105-120	73	—	—
ASO titer (u)	25	—	—	250-500	—	—
Blood Chemistries						
BUN (mg %)	54-19-28	28-35	35-36	49-70-62	88-146	170-212
Creatinine (mg %)	1.8-1.4-2.5	2.8-2.9	2.2-3.2	4.7-8.5-5.6	16.4	18.6
Uric acid (mg %)	8.2-5.4-6.9	5.4	5.4	5.2	9.4	—
Glucose (mg %)	126	—	—	—	—	—
CO ₂ (mEq/l.)	27.4-23.9	—	—	18.4-24	18.1-12.4	9.7
Chlorides (mEq/l.)	98-102	—	—	91-86	94-73	83
Sodium (mEq/l.)	141-129-134	—	—	125-130	130-107	123
Potassium (mEq/l.)	5.2-4.5	—	—	5.2-4.3	4.0-3.7	4.7
Albumin/Globulin (G %)	3.3/2.8-2.5/3.5	2.6/3.1-3.6/3.3	3.6/3.5	3.2/3.8-3.7/4.3	—	—
Cholesterol (mg %)	193	260	280	210	—	—
Alk. phos. (KA units)	12	18.5	—	—	—	—
Prothrombin time (sec.)	13/12.5	15/13	—	—	—	—
Calcium (mg %)	—	8.7	10.5	10.0	6.9	10.6
Phosphorus (mg %)	—	3.0	5.0	4.2	6.0	7.4

One month later, 14,500 ml of bloody fluid was again removed and the patient was given a unit of blood which was followed by an immediate febrile reaction. He was discharged after this subsided and he received some radiotherapy to the abdomen while he was home. The ascitic fluid quickly reaccumulated and he was

admitted after two weeks at home for another paracentesis. During the following three months, three paracenteses were done, each time with removal of about 10 liters of serosanguinous fluid. Each time the hemoglobin was slightly lower and blood was given. On the 6th admission, six months after surgery, the liver was felt to be enlarged and a large tender mass was felt in the right lower quadrant. PSP excretion was 8% in 15 minutes and 28% total. Cold agglutinins were negative, mucoprotein was 80 mg % and zinc sulfate turbidity 10.7 units. Nitrogen mustard was again instilled on the 6th admission and 200 millicuries of radioactive gold on the 7th admission.

Following the last paracentesis and instillation of the radiogold, the patient became weak and jaundiced. The abdomen had also rapidly become distended and the patient was readmitted for the last time ten days after the radiogold was given. He appeared chronically ill and jaundiced. Both lung bases were dull. The heart was pushed to the left and a systolic murmur was heard at the base and a diastolic murmur at the apex. A questionable pericardial friction rub was heard. Massive ascites was present with some ankle edema but no scrotal edema. Hemoglobin was 12.4 grams % and the white blood count 7,500 /cu mm with a normal differential count. The urinary sodium was 44 mEq, potassium 15 mEq and chloride 55 mEq. A paracentesis was done with removal of about five liters of bloody fluid. He developed severe hiccoughs which were not relieved by narcotics or sedatives. Two days later he was found dead.

*Dr. Samuel H. Klein:** In summary, we have a patient 53 years old who had diarrhea for three years. He developed intestinal obstruction which was overcome with a nasogastric tube. It was noted there was 3+ stool guaiac. He had a localized resection of 20 inches of terminal ileum with just a very small segment of the ascending colon, just above the ileocecal valve. He was well for a few months and then developed repeated accumulations of large quantities of bloody ascites, and he was treated with radiotherapy and nitrogen mustard and radiogold, and he also developed urinary symptoms.

In analyzing this, one would promptly consider some part of a malignant tumor because of the rapid accumulation of bloody ascites; the commonest cause of bloody ascites is seeding of the peritoneal cavity by malignant cells. Since our attention is directed toward the terminal ileum, one might further postulate that this patient had a carcinoma of the terminal ileum. This is by no means common, but it is possible for this patient to have had a malignant tumor of the terminal ileum with secondary peritoneal implantations.

However, in going back over the history, we realize that it is a very wrong history for carcinoma: diarrhea of about three years duration, and eight months of progressive obstruction. So that while carcinoma is possible, we have to look in other directions for the cause of this malignant seeding of the peritoneal cavity.

A carcinoid tumor is a possibility. Frequently these are benign but they may metastasize locally and generally, and if the peritoneum was seeded, I daresay that one might see this picture. This, however, is not usual.

Another consideration is a tumor such as a sarcoma perhaps originating in the

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mesentery itself and secondarily invading the ileum locally, causing ulceration with blood in the stool and then a progressive growth of the lesion to produce an obstruction. One might think of hemangiosarcoma, in view of the markedly bloody character of the ascitic fluid, although this type of tumor does not necessarily have to be present to produce bloody ascites.

One of the best possibilities is one of the lymphomas, namely, lymphosarcoma or Hodgkin's disease. We know that lymphosarcoma or Hodgkin's disease can occur both in a generalized form and a localized form, and may involve the intestinal tract locally. After its removal it can recur locally, and perhaps even generally, to produce the picture of ascites and some of the other signs that followed in this patient.

For example, this patient developed symptoms which perhaps might have occurred on the basis of involvement of the portal vein by invasion of either carcinoma or lymphoma. Also, pressure could have been produced retroperitoneally by extensive growth of lymphomatous tissue up and down the lumbar gutters involving some of the other structures and producing ascites. The mass which appeared in the right lower quadrant could very well go with recurrence of lymphoma or tumor tissue in the area of the resection, or an overgrowth of an implant of lymphoma or tumor tissue, or perhaps retroperitoneal nodes on the basis of one of these two types of tissue.

The enlargement of the liver could be accounted for by metastatic involvement by tumor tissue, or even by involvement by Hodgkin's disease or lymphoma. The appearance of jaundice may be explained either by extensive metastatic involvement of the liver, or by pressure on the extrahepatic biliary ducts by carcinomatous nodes.

It is difficult to tie the urinary symptoms, which became prominent in the later months, into the general picture. If there was extensive retroperitoneal growth of the tumor tissue, the vascular supply of the kidneys might become compromised either by pressure or invasion. On the other hand, this might very well be a simple pyelonephritis with an ascending infection, and then later uremia in a patient who had been catheterized many times. Or perhaps this is an independent glomerulonephritis causing late uremia, azotemia and blood in the urine with casts.

If this were not a primary intestinal lesion, and it was deemed inadvisable to do more than resect one area for diagnosis, perhaps short-circuiting might have been sufficient, had the surgeons known what the lesion was. But I can visualize a generalized intestinal lesion, lymphomatous in nature, causing intermittent obstruction and diarrhea. I doubt this, however, in view of the long history and the lack of symptoms.

One thing was available, if it were done, and that is examination of the ascitic fluid microscopically to determine the nature of the cells present.

I do not think this condition would fall under the category of a vascular disease of some sort. I know of no vascular lesion that would give infarctions, hepatic involvement and large masses all over the abdomen as well as ascites.

*Dr. Norman A. Samuels:** There was just one interesting point in the history

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and that was when the man first presented himself with diarrhea; his rectum on sigmoidoscopy showed granular mucosa. Cysts of *entamoeba histolytica* were demonstrated following treatment for which his complaints subsided for several months.

Dr. Klein: I have heard of carcinoma developing in regional enteritis. I personally have never seen a case, and if this case had started out as a case of non-specific enteritis, it is possible for secondary neoplastic degeneration to have occurred. That, of course, would be a primary focus for the ensuing metastatic disease.

*Dr. Vernon A. Weinstein:** Our preoperative diagnosis on admission here was regional enteritis.

Dr. Klein: On the basis of the clinical history, I would think so.

Dr. Weinstein: And on the basis of the x-rays which you have not had a chance to see yet.

Dr. Bernard Wolf:† Perhaps it was a good thing that you did not have the x-rays to see because I have more questions that these x-rays raise in my mind than answers.

I think that I can consider myself quite fortunate that I did not have the problem of x-raying this patient. He was quite heavy and the small bowel examination was apparently difficult on the two occasions it was done.

In the films taken several months earlier by Dr. Samuels and presumably interpreted as ileitis, there is a very long loop of small intestine which is about 18 inches in length and seems to occupy the mid-portion of the abdomen (Fig. 1). It cannot be localized because the loops of bowel seem to move around. It does not seem to be jejunum but neither does it seem to be ileum. It is obviously diseased with limited distensibility and peculiar diverticula.

There may or may not be separations of loops, presumably due to involved mesentery and lymphadenopathy.

There is still a maintenance of the mucosal pattern. It is not completely destroyed or distorted. I think I would have been a little uncomfortable. I would make the diagnosis of ileitis reluctantly but I could not have suggested a better diagnosis.

Something else to think about is segmental infarction of the bowel which could look like this. The cases of segmental infarction that we have seen have not usually involved as long a segment of the bowel as in this case.

The third possibility would be lymphosarcoma which occasionally can involve a large segment.

Five months later, however, the picture has changed. The loops are dilated and overlapping each other. However, whenever one finds dilated bowel and there is reason to suspect intestinal obstruction, one has to look hard for a stenotic site and I think I can find one. The lumen of the small bowel seems to come to a rather sharp demarcation with convexity proximally towards the dilated lumen

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FIG. 1. Small intestinal x-ray with right and left reversed showing peculiar loop of small intestine with diverticula.

and then there seems to be a streak of barium that extends down about three inches and then I lose it.

It would seem then that perhaps we have on this second examination a very localized, markedly stenotic, irregular segment of bowel, and perhaps this could be interpreted as being consistent with the ileitis which went on to fibrosis, stenosis and obstruction.

This is quite rapid for ileitis to do this because the interval was only five months. It could be interpreted, if this was vascular occlusion, as the terminal result with infarction, stenosis and obstruction. This would fit the timing somewhat better than stenosis due to ileitis.

Unfortunately, though, this is not the kind of stenosis that we see due to a segmental infarction which does not have an overhanging edge, but rather tapers in a funnel-shaped fashion into a narrow segment. It is the appearance of stenosis that we expect to see with a malignant infiltration.

If this is malignant tumor, it should not be lymphosarcoma because lymphosarcoma very rarely causes this kind of marked stenosis with obstruction. In one or two instances of lymphosarcoma, there was localized narrowing but I have not seen stenosis of this type.

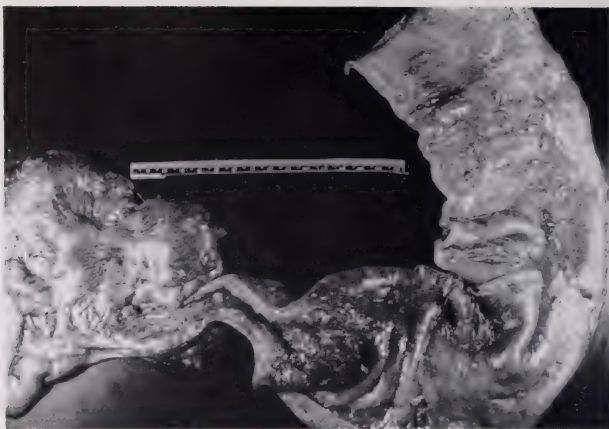


FIG. 2. Resected specimen of terminal ileum showing localized thickening of wall, narrowing of lumen and polypoid lesion to the right of the narrowing.

Whether this was primary carcinoma, I could not determine, or even if it were carcinoma, I would not know what the relationship of this is to all the apparent involvement that was seen five months previously.

Dr. Klein: I still feel as I did before. This is either one of the lymphomas, an adenocarcinoma or perhaps a sarcoma, either primary or secondary.

*Dr. Hans Popper:** Before we discuss the autopsy specimens of this markedly emaciated and severely jaundiced patient with a right rectus scar, five inches in length, we will describe the operative specimen.

The specimen was actually 55 cm of ileum, plus a relatively small portion of cecum and ascending colon (Fig. 2). The surgeon did not remove more of the colon because he found a perfectly normal appearing ileocecal valve, a normal appendix and normal mucosa of the large intestine. Approximately 5 cm proximal to the ileocecal valve, we found a marked thickening of the entire wall of the ileum with a very narrow lumen, obviously stenotic, with a granular appearing mucosa and then a polypoid lesion approximately 3 to 4 cm in diameter bulging forward into the lumen aggravating the narrowing. Proximal to this area we saw a greatly dilated ileum. There was no real ulceration in this part but a somewhat granular appearing mucosa. In the thickened and stenotic area with the polypoid mass, the mucosa was infiltrated by some bluish staining material which extended into the muscularis. The muscularis mucosa was hardly made out which means

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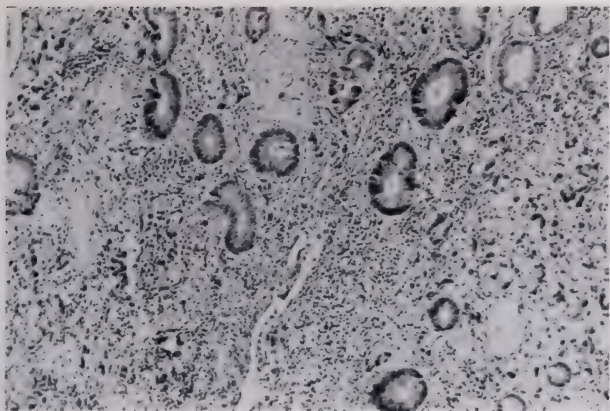


FIG. 3. Transition zone between tumor in ileum and non-tumorous area with glands in center part of picture.

we were not able to separate submucosa from the mucosa. The somewhat altered ileum, with many goblet-cells and rather globular cells showed a sharp transition in one particular area to a segment with mucus containing epithelial cells, rather widely separated and obviously a mucus producing carcinoma (Fig. 3).

Was this a metastasis from a carcinoma elsewhere or, as Dr. Klein has surmised, a primary mucus producing adenocarcinoma? This indeed is not an easy question to answer. In the operative specimen we found areas of proliferation of the glandular elements, irregularly arranged and obviously adenocarcinoma producing only a little mucus.

As we went deeper down into the bowel wall, we saw that the immature adenocarcinomatous cells looked almost but not yet malignant and becoming so in part of the circumference of the mass. Here was the heavy mucus producing area where the mucus was intracellular and extracellular.

In the deeper layers where these mucus producing cells were separated from each other, lying free in a gelatinous area which consisted of extracellular mucus, the cells appeared as signet ring cells. These mucus producing cells between the layers of muscularis burst eventually and discharge this mucus into the surrounding tissue, producing a colloid type of carcinoma.

We became a little surer that this represented a primary carcinoma when we looked at the polypoid area where we saw that the surface epithelium was not well differentiated and had grown in a polypoid or papillomatous fashion.

Therefore, from the specimen that was presented to the surgical pathologists, it appeared that the problem we were dealing with was one of the relatively rare cases of adenocarcinoma of the small intestine derived from the surface epithel-

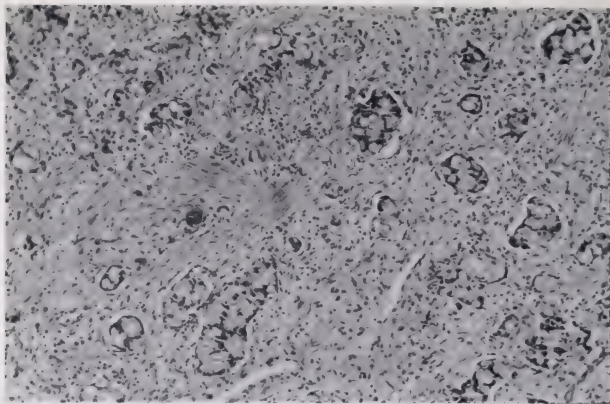


FIG. 4. Attempts at gland formation by tumor cells.

lium. Since the surface epithelium has mucus containing goblet cells, as the carcinoma grows down more and more mucus is produced, and in the depths it has the malignant character of a carcinoma spreading into the tissues and discharging large amounts of mucous material (Fig. 4).

We found invaded blood vessels and some lymphatic spread which diffusely involved the regional lymph nodes. Up in the mesentery the lymph nodes still were free.

Carcinomas of the small intestine are rare (1-5). They are found either in the jejunum or less frequently close to the ileocecal valve. Knowing their relative rarity, we looked for further confirmation as well as for a possible basis of the development of this lesion.

In an area of ileum close to the carcinoma we saw muscular hypertrophy in both the muscularis mucosa and the muscularis proper. Also a polypous type of arrangement of mucosa was noted in which the irregular epithelium replaced normal epithelium. Not only was the surface epithelium irregular but the glands were quite peculiar. They were partly colonic type of glands with a few goblet cells and filled with mucus (Fig. 5). Also other glands were different. They were the glands which we find in the duodenum. This was metaplasia of the epithelial lining in this area away from the carcinoma. These peculiar metaplastic glands contained apparently only neutral mucopolysaccharides. In this area of abnormal glands, there was piling up of epithelium almost to the degree of squamous metaplasia and the surface epithelium was entirely irregular with abnormal mucus production and on the surface some of the cells looked large and bizarre. We could not call it a cancerous type of cell but a precancerous one. Below this area there was severe inflammation. Many inflammatory cells were noted in this part of the

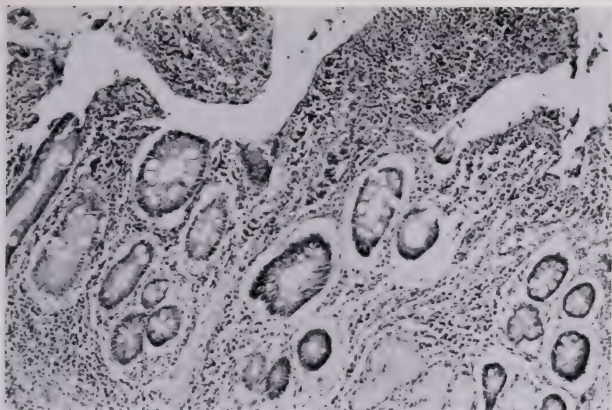


FIG. 5. Area of ileitis away from the tumor showing colon type glands and extensive inflammatory cell infiltration.

ileum and most of them were plasma cells indicating chronic, long-standing inflammation. This patient had a primary carcinoma in the ileum. Was it the result of the preceding ileitis? It is not a typical feature of regional ileitis. No pathologist would call this the scar producing type of regional ileitis, but it was apparently a chronic ileitis and with these chronic changes, I do not think that this was the secondary result of obstruction from the carcinoma. I would suspect that there was probably preceding ileitis reflected in the long-standing diarrhea and with nonspecific rather abnormal epithelial manifestations away from the area where carcinoma was present. Possibly this lesion was a precancerous one if this terrible term is in any way permitted. After the analysis of these surgical findings, I have now come to the question of what the autopsy findings were.

In the heart, little was seen except for some scars, probably on an atherosclerotic basis with thickened coronary arteries. The gross specimen of the lung was misleading. No significant changes were found but microscopically in the pleural lymphatics, mucus producing adenocarcinoma was seen with occasionally carcinomatous lymphangitis.

Esophagitis was present with destruction of the mucosa and other changes in the stomach obviously from vomiting. The stomach otherwise appeared normal. We found a nodule about 1 cm in diameter in the duodenum with some thickening of the underlying muscularis. Histologic sections quickly told us that this was an innocent lesion of no clinical significance. There was a large amount of bloody ascites in the abdominal cavity itself with seedings of carcinoma. The omentum was heavily impregnated by this mucus producing carcinoma as well as the entire mesentery (Fig. 6). The remaining ileum and the jejunum had perfectly intact

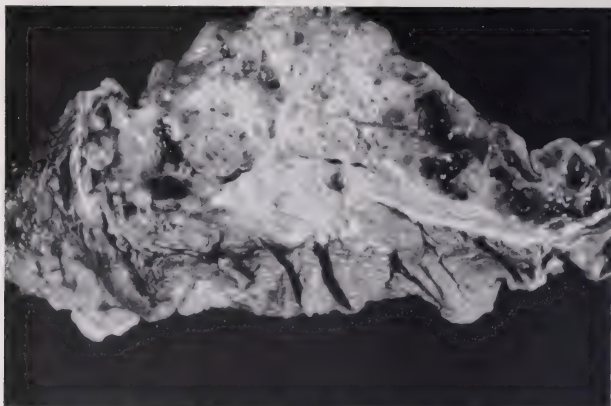


FIG. 6. Gross specimen of the mesentery showing extensive thickening and gelatinous appearance.

mucosa. The lymph nodes peculiarly enough in these areas were entirely free. We found carcinoma around the nodes whereas the lymph nodes themselves were free, confirming somewhat that the primary lesion was in the small intestine at the time of surgery where lymph nodes were involved. In the rectum, polyps were found. However, all these polyps were entirely benign. The retroperitoneal area was infiltrated by the tumor which extended around the adrenals and around the kidneys although the kidneys themselves grossly did not reveal any significant alteration except for bile pigment impregnation.

We have to assume that the terminal azotemia was most probably only in part related to renal involvement. What little there was may have been on a vascular basis but acute pyelonephritis was not present. It was to the greatest degree probably an electrolyte imbalance. In the veins of the kidney, carcinoma cells were found freely circulating.

The spleen was large, 400 grams, due to carcinomatous infiltration of the splenic vein. The spleen showed only passive congestion produced by this venous obstruction and this extended into the pancreas. The pancreatic alveolar tissue was infiltrated and replaced by carcinoma (Fig. 7). This carcinomatous alveolar tissue without involving the lymph nodes compressed the pancreatic duct and without involving the mucosa produced an obstruction.

The entire gallbladder was infiltrated by gelatinous tissue which extended into the hilum of the liver without involving the liver itself in this area and produced the terminal biliary obstruction without growing in the lymph nodes but in the soft tissue. The portal vein branches showed some terminal thrombosis.

The liver was huge, weighing 2800 grams. There was carcinoma infiltration but

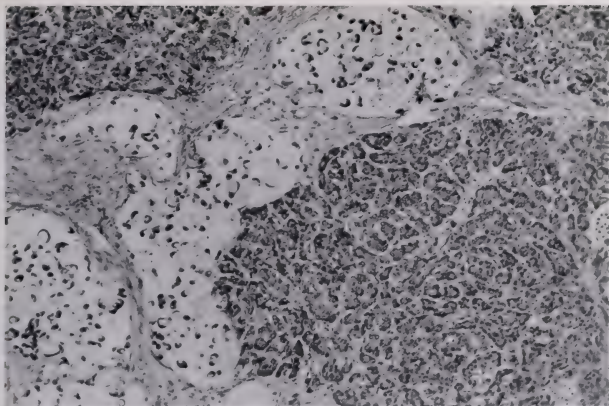


FIG. 7. Section of pancreas with extensive replacement of glandular tissue by mucus producing carcinoma.

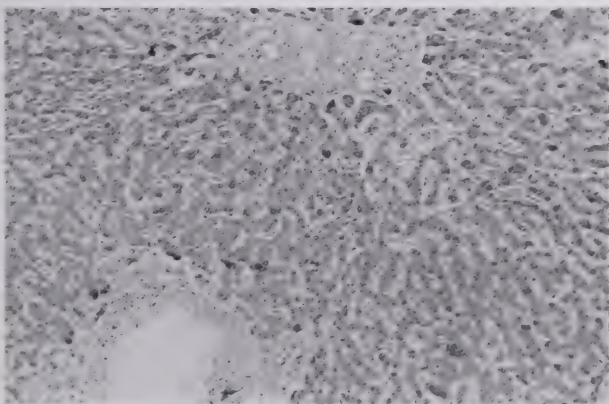


FIG. 8. Fibrosis around central vein of the liver lobule with destruction of the vein wall.

this could not be an adequate explanation for this marked enlargement of the liver. The architecture of the liver did not appear significantly altered. Some bile staining was present as we expected from obstruction at the hilum. Microscopically in the centrolobular zone there was extensive fibrosis (Fig. 8). These fibrotic

areas led to some narrowing of the central veins with passive congestion around them almost producing a Chiari-like syndrome. The central vein wall was in part destroyed. We looked for carcinoma tissue but none was found. Some periphlebitis with destruction of the vein walls was present.

I suspect that either nitrogen mustard or possibly the radioactive gold may have produced this kind of a lesion. I have not seen any evidence of this in the literature but I think we should look for such effects from the chemotherapy which is used.

In summary, this patient had a mucus producing adenocarcinoma of the terminal ileum. There was also a chronic ileitis. If it was the result or the cause, I am not quite sure. I suspect it was really the basis which produced the carcinoma. Nine months before death, intestinal obstruction developed which led to the operation. Bloody ascites was obviously a result of the peritoneal metastases although possibly the hepatic vein periphlebitis was a contributing factor to this severe ascites which with electrolyte imbalance was the final cause of death. Repeated paracenteses were done with the installation of nitrogen mustard and radioactive gold, and I suspect that this might have caused the hepatic vein branch periphlebitis which in turn led to the hepatomegaly.

Dr. Weinstein: We made the diagnosis at the operating table by means of frozen sections and the limited resection was done because there were implants in the pelvis at that time so that we had no thought of curing the man. The reason we did a resection at all was because we wanted to remove this mucosal lesion so he would not bleed. We believe that this was better therapy than just a sidetracking procedure. Our therapy of nitrogen mustard, purely palliative in type for the ascites, failed to palliate as far as the ascites was concerned.

*Dr. David A. Adlersberg:** I would like to comment on the possibility that the ileitis was a predisposing factor for this carcinoma in the terminal ileum. About two years ago we published two cases of jejunitis with carcinoma.

Dr. Burrill B. Crohn:† In the 800 cases of ileitis that we have in our files, we have only two cases of carcinoma in the small intestine, and those two cases were in areas where ileitis had been present or had been resected in areas contiguous to that. I would like to ask if this was true ileitis.

Dr. Popper: I am sure it was not. I hope I made it clear that it does not fit into the picture of regional ileitis. It did not extend into the submucosa at all and it in no way can be compared with regional ileitis.

Dr. Crohn: There was no clinical history of regional ileitis?

Dr. Weinstein: Diarrhea and obstruction were present and we in our naivete thought this was a case of ileitis that had gone to the obstructive phase but pathologically there was no evidence of it and at the operation it looked like a tumor and proximal to the tumor dilatation and obstruction were present but not ileitis.

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Dr. Adlersberg: These two cases that I referred to were typical granulomatous jejunitis.

Dr. Weinstein: I'm pleased that Dr. Popper recognizes other kinds of ileitis besides granulomatous ileitis.

Dr. Popper: This was of an inflammatory nature but I cannot prove definitely that the lesion may not have been the result of obstruction although we usually do not see this type of marked plasma cell reaction and aberrations of the glandular structure from obstruction.

From the floor: If the stenotic segment was not scarred, what did cause the stenosis? Also, Brunner type glands are said to be characteristically found in regional ileitis. Therefore, I feel that from some of the findings the ileitis was related to regional ileitis although it does not have all the features.

Dr. Popper: The stenotic portion showed clearly cancer separating the muscularis so that the stenosis was cancerous in the submucosa with no evidence of scars. As to the question of Brunner's glands, there was metaplasia in two directions: one was mucoid production and the other acid mucopolysaccharide production which is characteristic for any clinical inflammation. This led to variations in the metaplasia. I am sure that this glandular metaplasia is part of the picture of regional ileocolitis but I would reserve the diagnosis of regional ileitis for a characteristic pattern with scarring and granulomatous changes both of which were absent here.

Final Diagnosis:

(a) Mucus producing adenocarcinoma of the terminal ileum with extensive pulmonary, perirenal, peritoneal and intra-abdominal metastases causing ascites and biliary obstruction.

(b) Ileitis, type and etiology unknown.

(c) Periphlebitis of the hepatic vein branches.

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Radiological Notes

Pediatric Radiology

JOHN E. MOSELEY, M.D.

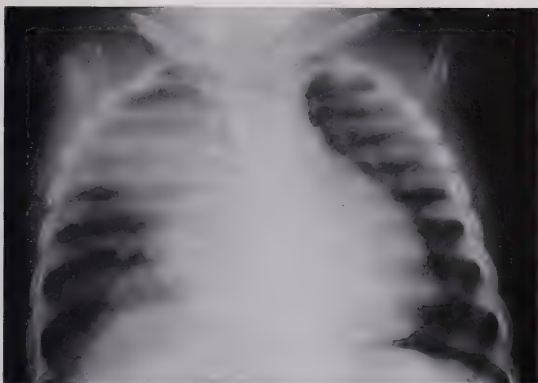
New York, N. Y.

CASE NO. 108

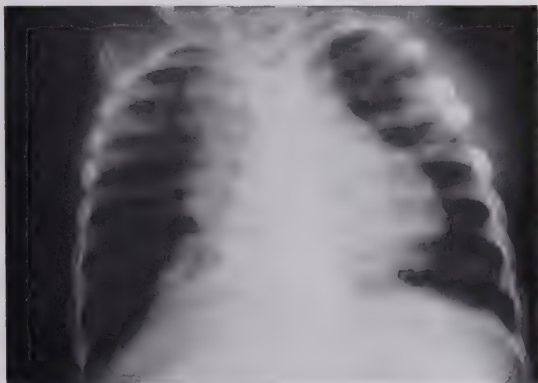
This was the first admission of a four month-old female infant whose chief complaints were running nose, cough, fever and difficulty in breathing. The onset of symptoms had been five days prior to admission and the respiratory distress had been increasing during the illness. The previous history revealed that a murmur had been heard at the age of a few weeks and the patient had been followed in the pediatric clinic where a diagnosis of patent ductus arteriosus was made.

Physical examination revealed a well developed and well nourished infant in respiratory distress with moderate retraction. Rhonchi were heard throughout the right chest and there were expiratory wheezes bilaterally. When the infant was quiet, a continuous murmur could be heard best near the left sternal border. The respiratory rate was 60 to 70 per minute, the pulse was 150 per minute and the temperature varied between 100 and 103°F. The intradermal test for tuberculosis was negative. X-ray examination of the chest was reported as showing a consolidation of the right upper lobe and patchy infiltrations extending into the right lower lung. The heart was enlarged. Pulmonary vascular markings were considered to be within normal. The medial half of the right diaphragm was elevated and on fluoroscopic examination showed paradoxical movement. The roentgen impression was that of partial eventration. The patient was treated with antibiotics and digitalized. The temperature returned to normal and the respiratory distress diminished considerably. Chest films, however, showed a persistence of the density in the region of the right upper lobe (Fig. 1). It was then considered that this density might well represent a large eccentric thymic shadow. Lateral and oblique projections of the chest were not conclusive and it was decided to administer steroids to the patient as a diagnostic test. The patient was given meticortin over a period of two weeks. A chest film made at the end of this time showed marked diminution of the density which had become more paratracheal in location (Fig. 2). Two weeks after cessation of meticortin, a chest film showed remarkable regrowth of the thymus, the shadow of which was practically similar to that demonstrated before the use of steroids. Two months after admission, division and ligation of a patent ductus arteriosus was performed.

The oral administration of corticosteroids to infants results in rapid atrophy of the thymus. When steroids are stopped, there is rapid regrowth and sometimes overgrowth of this gland. It is presumed that natural stress atrophy of the thymus is mediated through the pituitary-adrenal axis and regrowth and overgrowth are observed following stress atrophy in a fashion similar to that following



Case 108, Fig. 1. A homogeneous density is present in the region of right upper lobe. There is a small notch at the junction of this shadow with the right cardiac border suggesting that the density may represent a large thymic shadow. The medial half of the right diaphragm is elevated.



Case 108, Fig. 2. After two weeks of oral steroid therapy the thymic shadow has diminished considerably, the result of atrophy. The diaphragmatic eventration is clearly shown.

stoppage of steroid therapy. The thymolytic effect of steroids may be used to permit more accurate evaluation of the cardiac contour and supracardiac vascular images in instances where a large thymus obscures these shadows. It may also be of value in distinguishing between a large thymus and right upper lobe atelectasis, segmental pneumonic consolidation or loculated mediastinal pleurisy.

Final Diagnosis: THYMOLYTIC EFFECT OF STEROIDS IN INFANCY.

CASE NO. 109

This was the first admission of a nine year-old Puerto Rican male for diagnostic evaluation of growth and mental retardation and convulsive disorder. The child had been in the United States only five months prior to hospitalization. Among the patient's complaints was a history of diarrhea and abdominal pain and roentgen examination of the small bowel was made. Several long cylindrical filling defects were noted within the distal jejunum and proximal ileum. These



Case 109, Fig. 1. Small intestinal series shows coiled cylindrical filling defects within the barium filled lumen of the jejunum. Within these filling defects are curvilinear streaks of barium representing the contrast substance in the intestinal tract of *ascaris lumbricoides*.

were associated with curvilinear densities which appeared to bisect the lucent defects (Fig. 1). The appearance was that of unusually long round worms, the intestinal tracts of which contained ingested barium. The pattern and motility of the small bowel was otherwise unaffected. Examination of the stools for ova confirmed the presence of ascariasis.

The radiographic diagnosis of infestation with *Ascaris lumbricoides* can be easily made by barium studies of the intestinal tract. In some cases, moreover, the diagnosis can be achieved from a flat film of the abdomen on which positive shadows of the worms are contrasted against the gas in distended loops of bowel. In not all cases of roentgenographically demonstrated ascariades are ova found



Case 110, Fig. 1. Barium enema examination shows normal distensibility of the colon, no spiculation or shortening. There is a functional abnormality of the transverse colon indicated by irregularity of the haustral markings along the inferior bowel margin.

in the stool (male and sexually immature worms). The roentgen findings, especially those on the flat film, may be the first indication of the condition in children complaining of abdominal distress.

Final Diagnosis: INFESTATION OF INTESTINAL TRACT WITH *ASCARIS LUMBRICOIDES*.

CASE NO. 110

This was the first admission of an 8½ year old white female with a three week history of diarrhea. The patient was having three to four bowel movements a

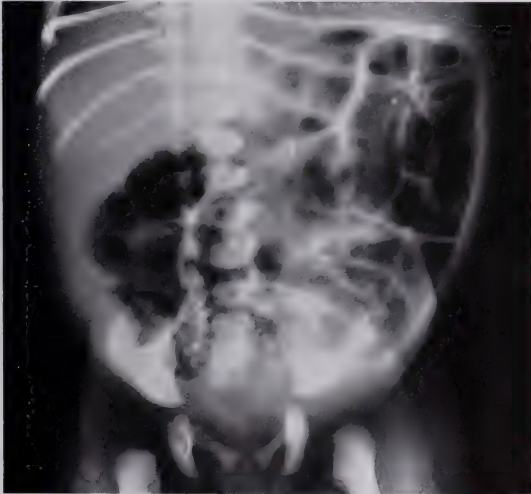


Case 110, Fig. 2. Reexamination of the colon 2½ months later shows shortening, coarse spiculation, polypoid hyperplasia of the mucosa and involvement of the terminal ileum. The process is diffuse and advanced.

day and her stools contained mucus and blood. The hemoglobin was 11.8 gms per cent, the sedimentation rate was 34 mm per hr. On admission she weighed 60 pounds. Stools were negative for amebae. A barium enema examination showed a normally distensible colon without serration or shortening but there was some irregularity of the haustral indentations in the transverse colon particularly along the inferior margin of its middle third. These findings were considered consistent with the very early radiographic changes in ulcerative colitis (Fig. 1). Sigmoidoscopy revealed mucosal changes compatible with ulcerative colitis. The patient was discharged to be treated at home.

Two and a half months later, she was readmitted because the bowel movements had increased steadily in frequency reaching a total of 10 to 20 a day on some occasions. Large quantities of blood and mucus were passed with the stools. The temperature ranged between 100° and 102°F and occasionally reached 103°F. On this second admission the patient weighed 46 pounds. A repeat barium enema after the 2½ month interval showed diffuse involvement of the colon by advanced changes which extended into the terminal ileum. There was coarse serration of the bowel margins, shortening, polypoid hyperplasia of the mucosa and loss of haustral markings (Fig. 2).

Ulcerative colitis occurs with increasing frequency between infancy and the age of 15 years. It has been reported to be a more severe disease in children than in adults, with a poorer response to treatment. Early adolescence appears to be a



Case 111, Fig. 1. Simple film of the abdomen shows gaseous distention of small and large bowel but there is no gas in the rectum.

particularly critical time for the appearance of the condition because of rapid progression and severe changes over short periods. The condition is twice as common in boys as it is in girls.

Final Diagnosis: RAPID PROGRESS OF ULCERATIVE COLITIS IN AN EIGHT YEAR OLD CHILD.

CASE NO. 111

This was the first admission of a three day old Puerto Rican male with the chief complaint of vomiting and obstipation since birth. The infant exhibited the typical features of mongolism. The abdomen was markedly distended. The clinical impression was that of intestinal obstruction presumably due to a congenital anomaly. A simple film of the abdomen showed gaseous distention of both the large and small bowel but there was a noteworthy absence of gas in the rectum (Fig. 1). The findings were consistent with a meconium plug syndrome or Hirschsprung's disease although the possibility of a high rectal or sigmoidal stenosis could not be excluded. Post-natal examination had shown no evidence of an imperforate anus. A digital rectal examination followed by a 5 cc saline enema resulted in the passage of a white mucous plug, strips of meconium and large amounts of gas. A Hypaque study of the gastro-intestinal tract, previously ordered, was carried through to 24 hours and showed distention of the small bowel and dilatation of the large bowel down to the sigmoid where there was an abrupt change in the calibre of the lumen which was normal or



Case 111, Fig. 2. Hypaque study of the gastrointestinal tract shows dilatation of small and large bowel. There is an abrupt change in calibre of the colon at the sigmoid. The sigmoid and rectum are smaller in calibre and represent the area of aganglionosis.

slightly diminished in size down to the anus (Fig. 2). The appearance was that of Hirschsprung's disease, the aganglionic segment involving the rectum and sigmoid.

The meconium plug syndrome is a non-specific syndrome found in the neonatal period. Meconium blockage may occur in normal but weak or premature infants, in cases of fibrocystic disease of the pancreas where the degree of meconium obstruction does not amount to actual ileus and it may result from the functional obstruction of Hirschsprung's disease. The clinical course following the passage of the meconium plug and the opening of the bowels will depend on the underlying cause.

Final Diagnosis: MECONIUM PLUG SYNDROME IN HIRSCHSPRUNG'S DISEASE.

CASE NO. 112

This was the first admission of a three month old male infant whose chief complaint was inability to move the right shoulder. In the history the mother



Case 112, Fig. 1. The right scapula is enlarged, thickened and sclerotic with loss of its normal contours. There are no changes in the clavicles or ribs.

stated that the child had been given "a polio injection in the right arm" and that the infant had been having pain in that extremity ever since. Physical examination revealed a soft tissue swelling over the right scapula, hypotonicity of the right upper arm musculature and tenderness around the right shoulder area including the soft tissue swelling over the scapula. Radiological examination of both shoulder girdles showed enlargement of the right scapula which was thickened and sclerotic (Fig. 1). The ribs and the clavicles were normal. There was a minimal periosteal reaction along the shaft of the right humerus. Laboratory studies revealed: Hemoglobin 9.0 gms per cent, WBC 14,200 per cu mm, ESR 75 mm per hour. The alkaline phosphatase was 33 K.A. units.

The x-ray findings were considered to be most characteristic of infantile cortical hyperostosis (Caffey) and the mandible was examined. It showed definite bilateral cortical hyperostosis (Fig. 2). Skeletal survey showed no other bony involvement.

Scapular lesions in infantile cortical hyperostosis are usually unilateral. They usually appear during the first six months of life. They should not be mistaken for malignant neoplasm as was often the case before the nature of the disease became widely known. Examination of other skeletal parts will usually show additional evidence of cortical hyperostosis. The mandibles are practically always involved and will confirm the diagnosis.



Case 112, Fig. 2. A.P. projection of the mandibles shows typical cortical hyperostosis.

Final Diagnosis: INFANTILE CORTICAL HYPEROSTOSIS (CAFFEY) WITH INVOLVEMENT OF THE RIGHT SCAPULA.

CASE NO. 113

This was the first admission of a newborn male infant who appeared lethargic at birth and sucked poorly. Nipple feeding was poorly taken and there was a cough on attempted swallowing. Because of the clinical impression of possible tracheoesophageal fistula, a tube was passed down the esophagus. It met no obstruction. A chest film made at the age of three days showed an infiltration involving the right upper lobe. An esophagogram and a tracheogram were normal. Subdural taps were negative. The patient continued to do poorly, experiencing numerous attacks of respiratory distress. At two months of age he was transferred to another hospital for supportive care. There, bronchography was reported as negative. Because of the continued feeding problem, he was readmitted to this hospital at the age of seven months. At this time he appeared weak and hypotonic. He was insensitive to pain caused by needle prick. There



Case 113, Fig. 1. There is a pneumonitis of right upper lobe partially obscured by residual Lipiodol from a previous bronchogram. There are also infiltrations extending into left upper lobe.

was excessive sweating unrelated to temperature or time of day. On excitement a diffuse blotchy erythematous rash would appear and the blood pressure would rise to systolic levels of 150 to 200 mm Hg. There were wide swings of body temperature from 98.8° to 105°F, apparently unrelated to episodes of pulmonary difficulty. A chest film at this time showed fine interstitial infiltrations throughout both upper lobes with some consolidation adjacent to the root of the right upper lobe. The latter was partially obscured by residual Lipiodol from the previous bronchography (Fig. 1). The roentgen appearance of diffuse interstitial infiltrations with persistent right upper lobe pneumonia was considered consistent with the clinical impression of familial dysautonomia (Reilly-Day syndrome).

Since no progress was made in correcting the feeding difficulty, the patient was again transferred for supportive care. He subsequently died following an attack of apnea and cyanosis.

Familial dysautonomia is an uncommon condition characterized by numerous manifestations of autonomic dysfunction in the circulatory, gastrointestinal, pulmonary and central nervous systems. Almost all cases reported to-date have been in children of Jewish extraction. One convincing exception has been reported by Linde (1). The condition appears to be transmitted as a recessive characteristic.

Pulmonary manifestations are common and occur to a significant degree in a majority of the patients. The roentgen findings are essentially those of a chronic bronchopneumonia. There are varying combinations of interstitial infiltration, atelectasis and, in infants, emphysema. In infancy the roentgen findings in the chest cannot be differentiated from those found in cystic fibrosis of the pancreas. After some months or years, however, the radiographic differentiation can frequently be made for in cystic disease of the pancreas the interstitial infiltrations are generalized throughout both lungs and there is a marked generalized emphysema. In dysautonomia the infiltrations are more scattered and generally do not involve the whole lung. As the child grows older emphysematous changes if present, tend to disappear. Bronchiectasis, which is often encountered in advanced cases of fibrocystic disease of the pancreas, is not seen in dysautonomia.

Patients with the congenital sex-linked form of agammaglobulinemia may show roentgen features quite similar to those seen in dysautonomia. In agammaglobulinemia, however, there is no hilar adenopathy. In fact, there is a deficiency of perihilar soft tissue density. This inadequacy of lymphatic tissue is generalized and may be demonstrated by lateral roentgenograms of the nasopharynx which show absent or deficient adenoid tissue.

It is considered that bronchial hypersecretion leads to bronchial obstruction with resultant pneumonia and atelectasis (2). Aspiration may also contribute to the pathogenesis of the pulmonary lesions.

Final Diagnosis: FAMILIAL DYSAUTONOMIA.

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Surgical Techniques

2. THE REPAIR OF INGUINAL HERNIA

JEROME W. CANTER, M.D., DAVID J. KAVEE, M.D., AND
IVAN D. BARONOFKY, M.D.

New York, N. Y.

The repair of inguinal hernias has long been the operation on which the novice surgeon begins his surgical career. The rather unfortunate classification of this operation as "minor" has given the impression that it can be done without an anatomical approach. Recurrences are quite common and, therefore, the anatomy of the area should be carefully outlined while doing the surgery. Actually, the procedure is one of complete anatomic orientation. The procedures to be described require the use of Cooper's ligament. We believe this approach to be anatomically correct. More exposure is necessary than with other repairs and, therefore, it probably takes a bit more time; however, this is offset by a lower recurrence rate. The procedure, as it is described, is suitable for adults. Hernias in infants generally require only ligation of the sac.

From the Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

The section on Surgical Techniques is one of a series prepared by the Department of Surgery. Some of the techniques described are original, others are of long-established application, some with modifications found useful here. The descriptions afford a concise review of techniques currently utilized at The Mount Sinai Hospital, New York.

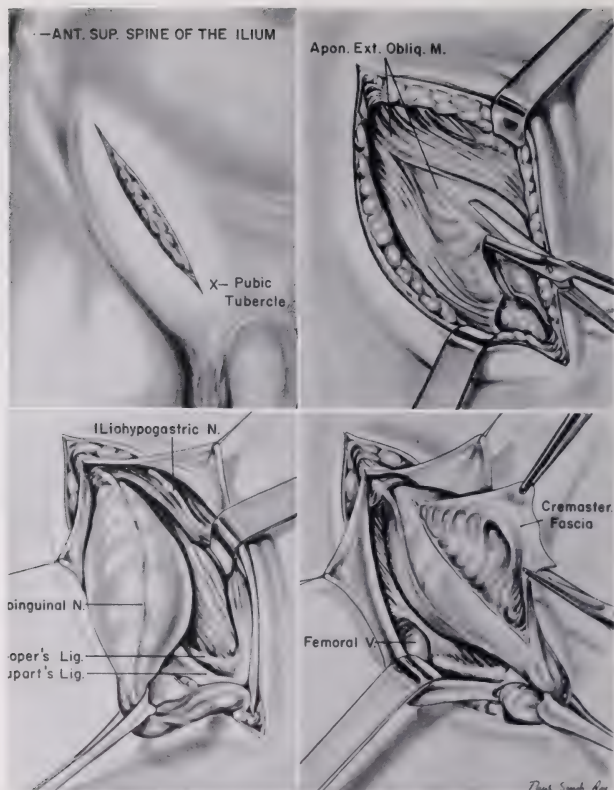


Fig. 1. The sketches are self-explanatory. Note the presence of Cooper's ligament at a plane deep to the inguinal ligament. The femoral vein lies under the lateral portion of the ligament. Note also the removal of the cremasteric fascia.

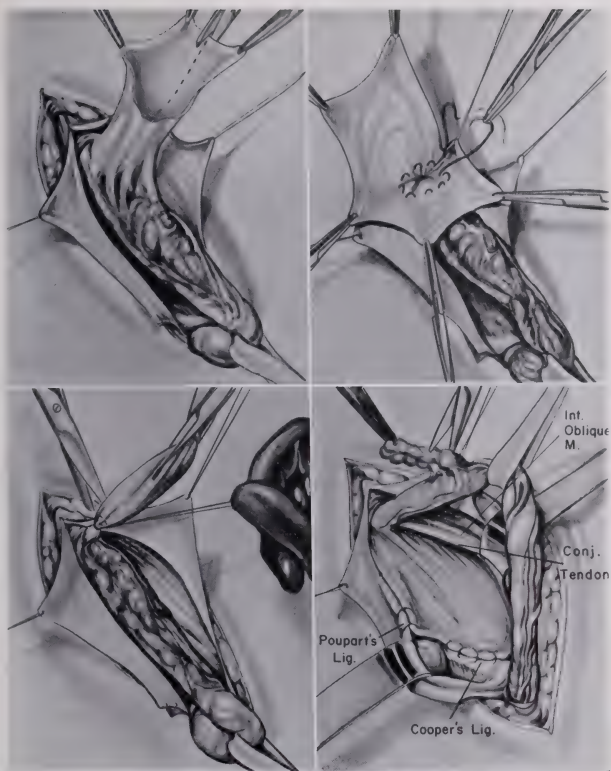


Fig. 2. The spermatic cord is cleaned thoroughly of excess fat and fascia. This will allow for a much more snug repair without impairment of the blood supply to the testicle. The later complication can occur if care is not taken. Note also the lateral extent of the Cooper's ligament repair (femoral vein) and the cross over to the inguinal ligament. The transversalis fascia should be used. If this is not available, then conjoint tendon is used.

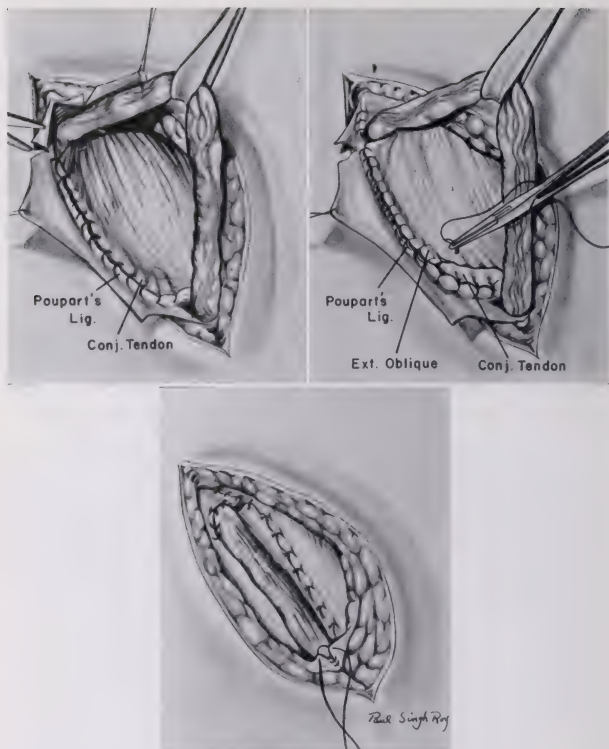


Fig. 3. The repair is completed by suturing the conjoined tendon and the medial leaf of the cut external oblique fascia to the inguinal ligament. The lateral leaf of the external oblique is then sutured under the cord, over both the previous layers.

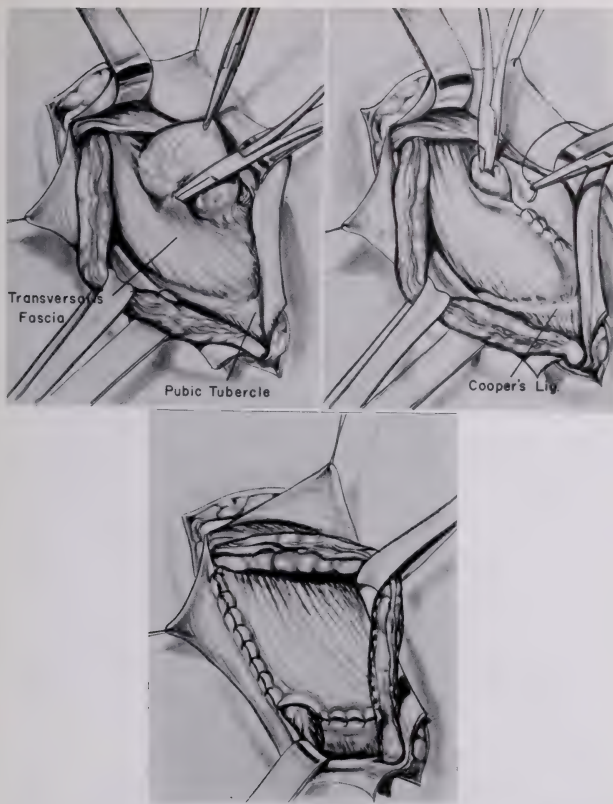


Fig. 4. The repair of the direct inguinal hernia is demonstrated. Note the defect is in the transversalis fascia.

Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital New York, N. Y.

Reflex Circulatory Effects Elicited by Hypertonic and Hypotonic Solutions Injected into Femoral and Brachial Arteries of Dogs. Richard Lasser, M.D., Douglas Allen, M.D., Myron Schoenfeld, M.D., Dimitri Lalossis, and Charles K. Friedberg, M.D. (From the Department of Medicine.) Presented February 15, 1960.

Circulatory responses to rapid intra-arterial (IA) and intravenous (IV) injections (femoral and brachial) of 3 to 80 ml of hypertonic and hypotonic solutions were studied in 14 adult mongrel dogs. Under deep Nembutal anesthesia, saline, dextrose, urea (75-2778 mOsm/L) and distilled water were given. IA pressures, heart and respiratory rates were continuously recorded. All IA hypertonic solutions caused a rise of heart rate, respiratory rate, and of systolic, diastolic, and pulse pressures in all animals. Responses began 6 to 8 seconds after onset of injection and lasted 2 to 5 minutes. Vasopressor responses occurred with as little as 5 ml of 5 per cent saline injected through an IA catheter wedged distally (1.25 mm diameter). A mean maximum pressure rise with 40 to 80 ml of 5 per cent saline was 38-18 mm Hg (range: 16-78-6-30 mm Hg); heart rate rise 18 min.; respiratory rate rose 134 per cent. Magnitude of response decreased with solutions of lesser hypertonicity. Isotonic solutions were without effect. Hypertonic solutions produced slight vasodepression. Arterial distention or occlusion painful stimuli and altered pH were not contributory. Intravenous hypertonic solutions caused vasodepression with increased pulse pressure and heart rate. Intravenous isotonic and hypotonic solutions were ineffective. Evidence was obtained excluding changes in central blood volume, cardiac distention, and vasomotor changes in the injected limb.

Abolition of the response could be achieved by sciatic nerve section of the injected limb while ipsilateral sympathectomy did not materially alter the response. It is suggested that these reflex responses to IA injection indicate the presence of peripheral receptors stimulated by changes in osmotic environment.

Hereditary Factors in Rheumatoid Arthritis. Arnold Goldenberg, M.D.* Jacques M. Singer, M.D.†, and Charles M. Plotz, M.D. (From the Departments of Medicine and Bacteriology, and the Department of Medicine, State University of New York College of Medicine at New York City.) Presented February 15, 1960.

A family study was carried out in order (a) to detect rheumatoid factor or related macroglobulins in kindred of rheumatoid persons by five serological tests and (b) to determine the value of these tests in hereditary studies. The study groups consisted of 106 relatives of 27 rheumatoids and 106 controls.

* Fellow, Arthritis and Rheumatism Foundation.

† Senior Investigator, Arthritis and Rheumatism Foundation.

Forty per cent of relatives and 13 per cent of controls were positive by at least one of the five procedures. Twenty-nine per cent of relatives and 7.5 per cent of controls gave a positive Euglobulin Inhibition Test. The Sensitized Sheep Cell Test yielded positive results among 14 per cent of relatives and 4.7 per cent of controls. The figures were slightly lower with the Euglobulin Sheep Cell Test. Less than five per cent of both groups were positive by the μ HL Latex Fixation and Sensitized Human D Erythrocyte Tests.

There was an equal distribution of positive results according to age group and relationship to the index rheumatoid case. Female kindred had a positive test by at least one method nearly twice as often as males.

The results indicate that kindred of rheumatoids have positive tests for rheumatic factor or related macroglobulins three to four times more often than controls. The Sensitized Sheep Cell, Euglobulin Sheep Cell and Euglobulin Inhibition Tests are useful procedures in genetic studies for rheumatoid arthritis.

The Interpretation of Altered Cell Morphology in the Relation to Tissue Changes. Herbert Nieburgs, M.D. (From the Cytology Laboratory.) Presented February 15, 1960.

The two fundamental factors in the evaluation of single cells in smears of secretions and fluids are the recognition of morphologic changes and the interpretation of such changes in the relation to the type and degree of histologic alterations. Since visual memory is inadequate for the extensive range of altered single cell morphology patterns, 61 criteria were developed for the examination of cell structures.

The recorded criteria and combinations of changes were correlated with tissue sections. In addition, planimetric measurements were carried out for all cell components.

The data obtained from this study led to a more precise interpretation of cellular changes than it is possible by visual memory. To increase further the accuracy, the combinations of criteria applicable to various tissue changes were incorporated into an electric memory system. Interpretations are made as to benign cells, inflammatory changes, degree of atrophy, active regeneration, hyperplasia, atypical hyperplasia and malignancy.

Hemodynamic Studies in Aortic Stenosis by Transbronchial Left Heart Catheterization. Alvin J. Gordon, M.D., Howard L. Moscovitz M.D., and Paul A. Kirschner M.D. (From the Department of Medicine.) Presented February 15, 1960.

Left heart catheterization by the transbronchial route is well suited to the study of aortic stenosis in the adult. In seven patients so investigated, it was possible to record pulses in left atrium, left ventricle and aorta, together with continuous pressure differences across the aortic valve and phonocardiograms.

The left ventricular pressure pulse in this disease is peaked. Pulsus alternans is relatively common. The central aortic trace is characteristic, with delayed upstroke, early systolic dip or anacrotic notch and late pressure maximum. Ejection

is prolonged and diastole shortened. The continuous pressure difference across the valve has the shape of an inverted V. In the cases here reported the maximum ejection gradient varied from 64 to 102 mm Hg; the peak systolic gradient from 43 to 95. The intensity envelope of the ejection murmur corresponded in shape and amplitude to the continuous pressure difference across the valve, which in turn is presumably proportional to the rate of flow across the valve.

Hemodynamic Effects of Balloon Obstruction of the Abdominal Aorta and Closed-Chest Extracorporeal Circulation in Experimental Myocardial Infarction with Shock. Leslie A. Kuhn, M.D., Frank Gruber, M.D., Albert Frankel, M.D. and Sherman Kupfer, M.D. (From the Division of Cardiology, Department of Medicine and the Department of Surgery.) Presented March 14, 1960.

The ability of extracorporeal circulatory support to produce a sustained increase in coronary perfusion pressure, and its effects on left ventricular work, cardiac output and systemic vascular resistance were investigated in closed-chest dogs with shock following plastic sphere coronary embolization.

In normal animals and in those with hypotension due to myocardial infarction, pumping of large volumes of blood (40-60 cc/kg minute) from the vena cava into the abdominal aorta failed to produce a rise in central aortic pressure.

To raise central aortic pressure in these animals it was necessary to increase vascular resistance. This was accomplished by inflating a balloon catheter inserted via a femoral artery into the abdominal aorta. Blood pumped from the superior vena cava supplied the distal aorta below the site of obstruction. In this manner, the circulation was "compartmentalized", leading to a rise in proximal aortic pressure with increased perfusion of the heart and the brain, and some diminution in distal aortic pressure. With this method, normal animals and those with myocardial infarction with shock demonstrated a sustained increase in central aortic (coronary perfusion) pressure and coronary flow, average central aortic mean pressure in 12 animals with shock rising from 73 to 139 mm Hg. Left ventricular end-diastolic and right atrial pressures remained normal. Left ventricular work diminished or remained unchanged despite the rise in central aortic pressure, due to shunting of a portion of the venous return into the distal aorta.

It is concluded that conventional techniques of extracorporeal circulation, employing shunting from the veins to the abdominal aorta, are ineffective in raising coronary perfusion pressure unless there is severe congestive heart failure. To raise aortic pressure by mechanical means in experimental myocardial infarction with shock, it is necessary to increase vascular resistance.

*Electrolytes in Gastric Secretion of a Patient with Complete Esophageal Obstruction and Permanent Gastrotomy.** Julius G. Parker, M.D.,† J. Lawrence Werther,‡

* Supported by grant A-2290 from the Inst. of Arthritis and Metabolic Diseases, U.S. P.H.S.

† Recipient of special fellowship in Gastroenterology, Montefiore Hospital, New York.

‡ Trainee in Gastroenterology, U.S.P.H.S. Training Program, Grant 2A-5126.

M.D. and Franklin Hollander, Ph.D. (From the Division of Gastroenterology, Department of Medicine, Montefiore Hospital; Gastrointestinal Physiology Research Laboratory and the Division of Gastroenterology, Department of Medicine, The Mount Sinai Hospital, New York). Presented March 14, 1960.

A recent study in this laboratory demonstrated the unequivocal sharp rise in potassium concentration [K] of human gastric juice after histamine stimulation. The possibility of contamination of gastric juice with potassium-rich saliva could not be completely eliminated. This problem was overcome in the present study on a single well-nourished patient with complete esophageal obstruction and a large permanent gastrotomy for 29 years. Following histamine stimulation [K] increased rapidly from basal values averaging 9.6 meq/L to a peak value averaging 21.4 mEq/L. After mecholyl there was a slight initial rise in [K] of 1 to 2 mEq/L above basal values followed by a sharp drop of 4 to 5 mEq/L by the end of the first hour post-stimulation. With sham feeding [K] showed but little increase above the spontaneous variation during prolonged basal secretion. Volume rate increase above basal levels was greatest with dinner sham feeding and least with mecholyl. Total acidity varied as high as 144 mEq/L.

All three stimuli caused an increase in potassium output; greatest after histamine and least after mecholyl. After histamine, sodium output fell sharply to a low plateau level, whereas after sham feeding and mecholyl stimulation it rose steadily.

These data demonstrated that (a) the rise in [K] previously reported was not due to salivary contamination; (b) the rise in [K] in response to vagomimetic stimulation was so small as to be equivocal; (c) there was no correlation between acidity and [K] nor between volume rate of secretion and [K].

Soft Tissue Radiography in the Diagnosis of Thyroid Carcinoma. Herman Zucker-
man, M.D., Eugene Friedman M.D., and Robert Lloyd Segal, M.D. (From
the Departments of Radiology and Surgery.) Presented March 14, 1960.

Soft tissue radiography has been used as a new diagnostic technique for the preoperative diagnosis of thyroid cancer.

The following criteria were used for differential diagnosis of calcifications appearing on x-ray:

Benign: Densely calcified, sharply defined, well margined, varied in size, haphazardly or individually spaced; if grouped, usually within a calcific rim.

Malignant: Not densely calcific, hazy, poorly margined, approximately similar in size, grouped in streaks or in a nebular formation within a well limited area but without calcific rim.

A clear differentiation was possible between benign and malignant calcifications.

Forty-five patients were studied by this technique. Of these, twenty-eight patients were subjected to surgery because of the presence of nodular goiters clinically suspicious of carcinoma. Six of these patients had thyroid carcinoma proven on microscopic section at the time of surgery. Three patients with thyroid carcinoma had positive x-ray findings for carcinoma. All three had

psammoma bodies found on microscopic examination of thyroid tissue. Seventeen other patients were studied. In eleven in whom the x-rays were negative, surgery has not yet been performed. In four patients with local recurrence of thyroid carcinoma, only one patient had a positive roentgenological examination. Two patients with carcinoma who had received radiation (I^{131}) to the thyroid gland prior to radiological examination, were negative on x-ray examination. There were no false positives.

The diagnostic implications of this method are discussed in relation to: (a) The preoperative diagnosis of thyroid carcinoma; (b) Location of a primary site in patients presenting with symptoms secondary to metastatic disease. This study is continuing and the results will be reported.

Spectrophotometric Determination of Azotyrosyl and Azohistidyl Residues in Azoproteins. Milton Tabachnick, M.D. (From the Department of Chemistry.) Presented March 14, 1960.

The coupling of diazotized arsanilic acid with bovine serum albumin (BSA) has been studied spectrophotometrically using the absorption spectra for the azobenzenearsonic acid derivatives of tyrosine and histidine. Fifty per cent of the protein bound arsanilic acid arsenic (As) was accounted for as azotyrosyl and azohistidyl residues when coupling was carried out at pH 9 or 10. When the ϵ -amino groups of lysine in BSA were blocked by acetylation (AcBSA) coupling at pH 9 resulted in azoAcBSA preparations, in which azotryosine and azohistidine accounted for 90 per cent of the protein bound As. These results indicate that, in addition to coupling with protein tyrosyl and histidyl residues, the diazo reagent is also bound extensively to the ϵ -amino groups of lysine.

In Memoriam

ERNST PETER PICK

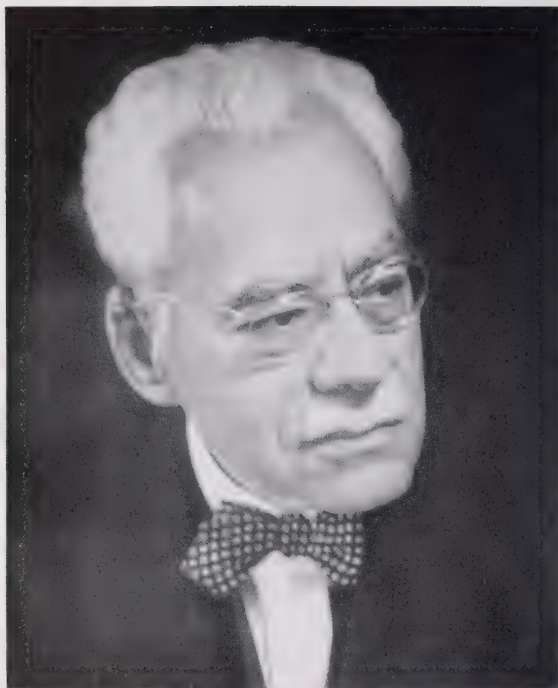
1872-1960

Professor Dr. Ernst Peter Pick was born in Jaromer, Bohemia on May 18, 1872 and died on January 15, 1960. He obtained his degree in medicine from the University of Prague in 1896 and spent the following three years in the Biochemical Laboratory of Professor Franz Hofmeister at the University of Strassburg and in the Medical Clinic of Professor Bernhard Naunyn. In 1899 he joined the staff of the State Serum Institute of Austria headed by Professor Richard Paltauf. During his stay at the Serum Institute he was first an assistant in, then adjunct, and finally Chief of the Biochemical Department. In 1904 he joined the Chemistry Faculty at the University of Vienna, attaining the rank of Associate Professor of Biochemistry. In 1911 he became first assistant in the Pharmacological Institute of the University of Vienna under Geheimrat Professor Hans Horst Meyer. He subsequently became Professor Extraordinarius and in 1917 Professor Ordinarius of Pharmacology and Toxicology. In 1924 he succeeded Professor Hans Horst Meyer in the Chair of Experimental Pharmacology and Directorship of the Pharmacological Institute and also held the post of Chief of the Research Institute for Drugs at the Governmental Health Department. From 1932 to 1937 he served as Dean and Vice-Dean of the Medical Faculty.

In 1939 he came to the United States at the invitation of Columbia University, College of Physicians and Surgeons as Clinical Professor of Pharmacology at Columbia University, retiring in 1946. In 1939 he became Associate in Pharmacology at The Mount Sinai Hospital, a position he held up to the time of his death. During this period he was also a Consultant to the Merck Institute for Therapeutic Research and conducted an active research program at that Institute in Rahway, New Jersey.

In 1957, on the occasion of his eighty-fifth birthday, he was awarded the Great Silver Cross of Merit of the Republic of Austria and the Schmiedeberg Plakette, the highest honor of the German Pharmacological Society.

Professor Pick was a pioneer in immunochemical research and as early as the first years of the twentieth century isolated immune bodies from serum, separated globulins and showed that azo compounds could produce antibodies. He demonstrated an awareness of the basic and multifaceted importance of immunochemical research and laid the groundwork which provided not only the initial but much of the sustained impetus for studies in this important area. Investigators drawn from many scientific disciplines flocked to his institute in order to benefit from his teachings and to learn the new techniques which he provided for the understanding of the chemical nature of antigens. Science is still intrigued by the ramifications of his fundamental observations which provided more than a mere show of flashy prestidigitation. His section on the chemistry of antigens in the *Kolle-Wasserman Handbuch* still remains a classic.



DR. ERNST PETER PICK

1872-1960

It is remarkable that even in his retirement he conducted important investigations on the adrenal gland and its steroids. To list all of his publications would be a monumental project.

It is apparent that Professor Pick was the type of individual who was not limited by the boundaries of his immediate scientific discipline. He firmly believed that all scientific fields overlap and that interdisciplinary application is necessary in order to obtain a maximum of knowledge and understanding.

The students of Professor Pick, numbering many hundreds and located in key positions throughout the world, owe an incalculable debt to their mentor. From the very inception of his career he typified the patient teacher, giving generously, liberally and, even more important, graciously of himself. All of his students learned much of pharmacology and experimental therapeutics, but of most benefit was the opportunity the association afforded them to observe greatness and altruism in so creative a person. Professor Pick took more personal pride in the progress of his students than in his own work. The months spent with him were productive not alone in scientific knowledge but also in the richness of human understanding.

WILLIAM ANTOPOL, M.D.
for the
Editorial Board

IDIOPATHIC HYPERLIPEMIA AND DIABETES MELLITUS. DEVIATIONS FROM NORMAL LIPID METABOLISM

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INTRODUCTION

Metabolic alterations in the handling of dietary lipids have long been associated with diabetes mellitus and idiopathic hyperlipemia. Recent studies have focused on specific defects in metabolic pathways. In diabetes mellitus, disturbances in fat metabolism are apparently acquired, and are related to a deficiency of reduced triphosphopyridine nucleotide, reflecting chiefly a retardation of glucose utilization by the hexosemonophosphate shunt. In idiopathic hyperlipemia, the responsible lipid metabolic defect is apparently inborn, and results in an inability to transport circulating lipids at a normal rate. This abnormality is, in part at least, related to the activity of a plasma lipid clearing factor, lipoprotein lipase, and perhaps to a lipid mobilizing substance elaborated by the pituitary gland. The significance of chronic, relapsing pancreatitis in idiopathic hyperlipemia is still uncertain, but appears to be a result, rather than a cause of the disorder.

Normal lipid metabolism is reviewed, and is contrasted with that seen in diabetes mellitus. The biochemical, pathogenetic, clinical, and therapeutic features of idiopathic hyperlipemia are discussed in detail, and the differentiation of diabetic hyperlipemia from idiopathic hyperlipemia is outlined.

SYNTHESIS AND OXIDATION OF FATTY ACIDS

As dietary fat enters the gastrointestinal tract, alimentary lipases hydrolyze the fat to form fatty acids, which are absorbed and esterified by the intestinal mucosa, and carried to the blood stream, mainly as lipoproteins (chylomicra), as well as phospholipids and cholesterol esters for distribution to the tissues (1). A "priming" or "sparking" activation reaction then occurs, whereby the fatty acid is converted to a fatty acyl derivative of coenzyme A (CoA), associated with an oxidative phosphorylation and production of adenosine triphosphate (ATP) (2, 3). The formation of this active fatty acid is accomplished by several enzymatic processes, each involving the formation of acetyl CoA or fatty acid derivatives of CoA. The former is derived from pyruvic acid oxidation, as well as by replacement of the succinyl group of succinyl CoA by short-chain fatty acids and β -ketoacyl CoA cleavage by CoA. Fatty acyl CoA is formed by the same enzymatic cleavage process of β -ketoacyl CoA, as well as by the action of ATP on fatty acids (2).

After this activation, fatty acid oxidation may then take place, in the presence of a free carboxyl group. Oxidative enzymes from mitochondria in the liver catalyze the process of β -oxidation, and the component reactions are reversible.

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The basic reaction by which energy is formed involves successive cleavage of two-carbon fragments in peripheral tissues, which either enter the tricarboxylic acid (TCA) cycle directly, or condense in the liver to form ketone bodies, which are then carried to the periphery to be oxidized by the TCA cycle (3, 4, 5, 6).

Fatty acid synthesis and breakdown cannot proceed without acetyl CoA as an intermediate. Any source of acetyl CoA is an adequate substrate. Fatty acids may then be synthesized from carbohydrate, by the decarboxylation of pyruvate in the presence of CoA (or from other acetyl CoA precursors). Protein also may convert to fatty acids with CoA. Ketone bodies formed in the liver, when released in the blood stream, may be oxidized to a CoA derivative, from which acetyl CoA may be obtained to serve as an initial building block in the formation of fatty acids (3). The enzyme system in rat liver which catalyzes the incorporation of acetate into fatty acids requires both triphosphopyridine nucleotide (TPN) and diphosphopyridine nucleotide (DPN). Reduced DPN is necessary for most of the reduction reactions in fatty acid synthesis (7). Reduced TPN is necessary for the reduction of crotonyl CoA to butyryl CoA (8).

As β -ketoacyl CoA cleavage occurs, the cycle of fatty acid metabolism is perpetuated: the fatty acyl CoA formed undergoes β -oxidation again, while the acetyl CoA synthesized re-enters the TCA cycle by condensation with oxalacetate. High fat intake in rats accelerates the rate of acetate oxidation and, perhaps, acetate production from β -oxidation of fatty acids, but oxidation of the substance into which acetate is incorporated is not increased (9).

The dependence of lipogenesis on carbohydrate metabolism (*i.e.*, on glucose utilization) is well established (1, 2, 6, 10-26). Bragdon has shown that, of injected labeled chylomicra, fasted rats expired 45 per cent of $C^{14}O_2$, whereas carbohydrate-fed rats expired less than 5 per cent in 90 minutes. In fasted rats, metabolism of chylomicra and nonesterified fatty acids (NEFA) proceeds at approximately the same rate, and carbohydrate feeding markedly diminishes the oxidation of palmitic acid administered as chylomicra or as NEFA (13). The sparing action of carbohydrate on fat metabolism is thereby demonstrated. Its mechanism of action has been attributed, by Lossow *et al*, principally to direct restriction of the enzymatic degradation of fatty acids to smaller molecules, as witnessed by measurements of injected labeled fatty acid. Except for a small fraction, carbohydrate does not apparently divert acetyl CoA from an oxidative to a synthetic pathway. This sparing effect is observed on all even-carbon fatty acids, with carbohydrate exerting a greater influence as the chain length increases (19). Chylomicra disappear from the serum just as rapidly with carbohydrate feeding (13), and their removal *in vitro* has been demonstrated in muscle (27), kidney (16, 28), and heart (28), as well as in liver.

TRANSPORT OF FATTY ACIDS

Circulating Lipid Fractions

Once fatty acids enter the circulation, they are transported in the plasma in both an esterified and non-esterified form. More than 90 per cent exist as glycerol esters or more complex alcohols, such as cholesterol. Of this fraction, about

80 per cent is equally divided between triglycerides (neutral fats) and phospholipids, and the remainder exists as cholesterol esters. The non-esterified (or un-esterified) fatty acids are in low concentration (about 5%), but are highly active physiologically, with a turnover velocity half-time of about two minutes (14). They are composed essentially of long-chain fatty acids (16–18 carbon compounds in 85%) (29).

Most of the plasma lipid in the human adult migrates with the β -globulin fraction of the serum on paper electrophoresis, and is, consequently, referred to as β -lipoprotein. These are mostly low-density lipoproteins of the class $S_f(0-12-30)$. The low-density lipoproteins of $S_f > 12$ are α_2 -lipoproteins. The β -lipoproteins contain triglycerides, sterol esters, and phospholipids, whereas α -lipoproteins are low in triglyceride content. As the density of the lipoprotein molecule decreases, there is a corresponding increase in triglyceride and decrease in phospholipid, cholesterol, and protein. Thus, in the low-density β -lipoproteins, triglyceride accounts for about 25 per cent of the fatty acid present, the remainder being distributed between cholesterol esters and phospholipid. In contrast, the high-density α -lipoproteins have about 50 per cent protein, 25 per cent phospholipid, 20 per cent cholesterol (mostly esterified), and only less than 10 per cent triglyceride (30).

Chylomicra, which represent the stable, lactescent lipid emulsion found in the intestinal lacteals, are largely triglyceride, and apparently carry a negative charge, since they can be flocculated by protamine or toluidine blue (30–32).

Non-Esterified Fatty Acids

NEFA in plasma are derived primarily from adipose tissue, as well as from hydrolysis of plasma triglyceride and from the gastro-intestinal tract and lymph (33, 34). Measurements of the arterio-venous differences from the greater saphenous vein point toward its drainage area (primarily adipose tissue) as the major source of circulating NEFA (33, 35, 36). These fatty acids are bound to the plasma albumin to maintain solubility, and serve not only as a highly efficient transport mechanism for fatty acids under normal circumstances, but also as a substrate during a fast for cellular oxidation and energy production in most tissues (14, 29, 30, 32, 35, 37–40). NEFA depend on albumin *in vitro* for their release from adipose tissue, as well as for lipolysis. The release of esterified fatty acids (*i.e.*, the mobilization of glycerides), on the other hand, requires the presence of β -lipoprotein *in vitro* (41).

Intravascular Hydrolysis of Fatty Acid

Several mechanisms of fat transport have been suggested, and partially elucidated. The most prominent, perhaps, is that of triglyceride hydrolysis by a tissue enzyme, lipoprotein lipase (or clearing factor). This substance has been found in greatest quantities in adipose tissue (42), as well as in heart (42), and, to a lesser extent, in plasma, liver, kidney, spleen, and lung (30, 43). Skeletal muscle and aorta are apparently devoid of this enzyme. This correlates well with observations that most of the transport of fatty acid from blood to tissue

occurs in the liver (35) and the myocardium (37), as measured by arterio-venous differences of total fatty acids. Lipoprotein lipase (LPL) is activated by heparin, destroyed by liver, and inhibited by protamine. *In vitro* studies by Korn and Quigley show that LPL is inactive in the absence of any added cation. Activation may be accomplished by a small concentration of Ca^{++} (or Sr^{++}), and NH_4^+ , Mn^{++} , or Mg^{++} (42). Higher concentrations of NH_4Cl and $(\text{NH}_4)_2\text{SO}_4$, as well as any concentration of Na^+ , K^+ , Li^+ , Rb^+ , $(\text{CH}_3)_4\text{NCl}$, and Ba^{++} are inactive or inhibitory in action. A fatty acid acceptor in plasma is essential for the activity of LPL. Korn believes this to be either albumin or Ca^{++} (43). Bergström and Borgström are in accord, but feel that in addition to albumin, α - and β -lipoprotein are necessary (44). According to Seifter and Baeder, all, including Ca^{++} , are required (45). In either event, increased binding of fatty acid to albumin and to lipoprotein is observed in the presence of LPL (44). Anfinsen postulates the need for available free binding sites, specific for fatty acids, on the albumin molecule, as well as an unknown serum "coprotein (46)". Moreover, he infers that heparin is a component of LPL. This is founded upon the ability of protamine to inhibit LPL activity, and the subsequent reversal of inhibition by heparin. Further support is based on the stimulation of LPL plasma activity by anaphylactogenic agents in dogs, which is presumably related to heparin and histamine secretion by mast cells. In these animals, prior antihistamine administration prevents shock, but the LPL rise still occurs; subsequent administration of small amounts of protamine will cause the enzyme to disappear from the circulation (46, 47). Havel and Bragdon, however, assert that heavy anions other than heparin may stimulate LPL activity (48).

The clearing reaction itself is poorly understood. Once chylomiera enter the blood from the intestinal lymphatics, removal normally is rapid. The clearing reaction occurs almost immediately, and increases the rate of fat removal (49). LPL acts specifically on ester linkages in triglycerides (50), and by progressive removal of triglyceride from chylomiera and the more soluble lipoproteins, [as well as from artificial fat emulsions activated by α -lipoprotein (51)], low-density lipoproteins are transformed into ones of higher density (1, 46, 47, 52), and the liberated fatty acids are carried in the NEFL fraction by albumin until entry into tissue cells for oxidation is possible (53, 54). The cleared cholesterol apparently undergoes direct transfer from Kupffer cells to hepatic cells for excretion in bile as cholesterol or bile acid, or for secretion into plasma as lipoprotein (53). Associated with the clearing reaction is an augmentation of triglyceride fatty acid oxidation (49). C^{14} fixation *in vivo* after a labeled fat meal in rats indicates that the action of heparin is to accelerate movement of fat from the blood to the tissues (49).

Most evidence seems to favor the greater importance of triglyceride hydrolytic activity at the tissue cell surface (or within cells) (30, 54, 55), rather than intravascular hydrolysis alone (1, 38, 54), particularly since the surface-active agents, Tween 80 and Triton A20 or its derivatives, will delay removal of injected lipid particles from the blood in normal animals (55). Zilversmit feels that heparin administration or hyperlipemia may cause overflow of LPL into plasma,

with a resultant increase in intravascular lipolysis (54). Bragdon states that the bulk of the chylomicra is removed intact from the circulation. Most is found in the liver after a fast, whereas, after a carbohydrate meal, the majority is transported to the fat depots (13, 56).

Extravascular Hydrolysis of Fatty Acids

Perhaps the primary significance of the clearing reaction is extravascular, since LPL originates in adipose tissue and certain viscera (42). There is evidence that lipoproteins and chylomicra can enter thoracic and hepatic lymph apparently intact, either through "pores" in the semipermeable capillary membrane directly or via phagocytosis by reticulo-endothelial cells, or by direct transfer from blood to liver cells at discontinuous, or fenestrated, areas of sinusoidal endothelium (38, 57). Hepatic transport, as measured by chylomicron concentration in hepatic lymph, apparently is related to both blood concentration of chylomicra and portal venous pressure (38). In addition, the rate of fat transport will diminish after hepatectomy (30). It has also been demonstrated that adipose tissue will take up both triglyceride and NEFA from albumin solutions and blood NEFA are also found intact in adipose tissue, lending credence thereby to the "pore" theory of capillary permeability, since no direct contact between adipose tissue and blood is believed to exist (32, 38, 55). However, the NEFA-albumin complex may also dissociate at the endothelial cell surface, with fatty acid leaving the blood by way of the endothelial cells, rather than by diffusion through pores (38). Since triglyceride uptake by tissue cells can be inhibited by sodium fluoride, an active transfer process is suggested. Perhaps some lipolysis normally occurs at tissue cell interfaces with selective removal of triglyceride (55).

That the function of albumin as one purely of transport is attested to by the observation that NEFA must first be dissociated from albumin before they can enter the tissues from the circulation (30, 32, 38). In studies with ascites tumor cells, the fatty acid-albumin complex is absorbed from the medium onto the cells by a passive partition process between the medium and the lipids of the cell surface (32). Fatty acid is separated from albumin, and the albumin is neither absorbed onto the cell wall nor transported across the cell membrane.

Phospholipids, Cholesterol, and Erythrocytes in Fat Transport

The fate of phospholipid is such that it plays an insignificant role in lipid transport (30). Only a small portion of dietary fatty acid reaches the blood as phospholipid, since ingested phospholipid is degraded in the intestines to diglycerides and other compounds. Some phospholipid, but mainly triglyceride, is resynthesized from diglyceride by esterification. Once in the circulation, phospholipids exist exclusively as components of the lipoprotein complexes, and only as such, serve as vehicles in triglyceride transport. Under conditions resulting in impaired carbohydrate utilization, phospholipids may act, in extraintestinal tissues, to mobilize fatty acids (30).

Cholesterol is of minor consequence in lipid transport, since turnover is accomplished at an extremely slow rate, based on the rates of incorporation of acetate into the fatty acids of the plasma esters (30).

By P^{31} studies, Turner has shown that erythrocytes do not participate in fat transport (58). However, *in vitro* observations by Fillerup *et al* demonstrate fatty acid synthesis in erythrocytes, with the release of these lipids into the medium, only in the presence of α -lipoprotein (32).

SUMMARY

The ultimate result of fat transport normally is one of equilibrium between lipid lost from the liver—by intrahepatic oxidation, secretion as lipoprotein, and excretion in bile—and lipid accumulated by the liver—from endogenous synthesis and uptake from the periphery (53).

Fat transport is dependent on several mechanisms, acting simultaneously, according to current conceptions. A tissue enzyme, lipoprotein lipase is elaborated by certain viscera, particularly adipose tissue, to attack ester linkages in triglycerides. The fatty acids thus derived from chylomicra are bound to albumin and transported in the relatively small, but intensely active NEFA fraction to the tissues for utilization. Whether triglyceride hydrolysis principally occurs within the blood stream, at the cell surface, or in the tissues, remains indiscerned; recent observations, however, suggest that such activity at the tissue cell surface predominates.

FAT METABOLISM IN DIABETES MELLITUS

Ketogenesis and Ketosis

Ketogenesis occurs only in the liver, with long-chain fatty acids as the principal substrate. Although certain amino acids may also be converted to ketone bodies, carbohydrate does not represent an available source (6). The mechanism by which ketone acids are formed involves fatty acid breakdown to the 4-carbon stage, with deacylation to acetoacetate in the presence of a catalyst, acyl CoA deacylase. In the liver, CoA is irreversibly cleaved from the carboxyl group of acetoacetyl CoA; in the periphery (particularly myocardium and kidney), reversible cleavage occurs by succinyltic deacylation (3). This deacylation reaction exists in balance with a process of activation of the 4-carbon fragment by CoA, with the resultant production of acetyl CoA, which ultimately enters the TCA cycle by condensation with oxalacetate. The ketone bodies, once formed from fatty acid oxidation in the liver, then enter the blood stream for transportation to the extrahepatic tissues for utilization and consequent energy production.

In diabetes mellitus (or fasting), it is generally accepted that defective carbohydrate utilization is the metabolic error responsible for excessive ketogenesis, or ketosis. This abnormal rate of ketone body formation is apparently an attempt to satisfy the energy requirement of body metabolism. It may also favor conservation of the available glucose for consumption by the central nervous system, which apparently is incapable of utilizing ketone bodies (4).

Effect on Fat Synthesis

Ample verification has been offered to show that this error in carbohydrate utilization is also responsible for inhibition of fatty acid synthesis from acetate in the diabetic liver (1, 2, 11, 12, 14, 15, 18, 19, 22–26). The precise biochemical

failure in diabetes remains a source of controversy. A specific defect in glucose phosphorylation is repeatedly implicated (6, 8, 14, 59, 60, 61). Gurin gave impetus to this concept when he demonstrated the inability of aqueous extracts of diabetic rat liver to synthesize fatty acids, in contradistinction to normal liver extracts (17). When glucose, normal liver mitochondria, or diabetic liver supernatant is added to diabetic liver extracts, this defect is not corrected. However, addition of normal liver homogenate supernatant, butyryl CoA, or glucose-6-phosphate (with or without ATP) will stimulate lipogenesis. The most striking provocation of fatty acid synthesis is achieved by the added presence of glycogen, hexose diphosphate, and fructose (17, 25). Since butyryl CoA can apparently replace aqueous diabetic and normal liver supernatant, the defect in diabetes was thought to represent a lack of cofactor(s) necessary for the conversion of acetyl CoA to butyryl CoA, thereby preventing the transformation of pyruvate, acetate, or acetyl CoA to fatty acids (6, 61).

Langdon then showed that incorporation of acetate into fatty acids in rat liver has an absolute requirement for reduced TPN, as well as for reduced DPN (8). He, and later, Shaw *et al.*, demonstrated the site of action of TPNH₂ to be at the stage where crotonyl CoA is reduced to butyryl CoA, an enzymatic process which cannot be catalyzed by DPNH₂ (26). It becomes evident that fatty acid synthesis depends on normal glucose metabolism for production not only of acetyl CoA, but also for reduced DPN and reduced TPN.

Since the Embden-Meyerhof glycolytic pathway produces DPNH₂ but no TPNH₂, attention has been focused on the phosphoglucuronate oxidative (pgo) pathway (hexosemonophosphate or phosphohexose shunt), by means of which reduced TPN is generated (7, 60). Siperstein and Fagan demonstrated the predominant dependence of fatty acid and cholesterol synthesis on glucose oxidation in the pgo pathway by studies of labeled acetate incorporation into cell-free, normal rat liver homogenates (62, 63). Small, but significant rates of lipogenesis and cholesterol formation were maintained by these homogenates alone, without any added coenzymes. However, stimulation of Embden-Meyerhof glycolysis by added DPN moderately augmented the rate of fatty acid synthesis, up to 37 times the control, while failing to alter significantly the rate of cholesterol synthesis. When the pgo pathway was accelerated by the addition of TPN, both fatty acid and cholesterol synthesis increased markedly: an average of 102 times the control for the former, and 293 times the control for the latter. A combination of these metabolic stimuli effected an even greater enhancement of fatty acid synthesis, while cholesterol synthesis was depressed to a level somewhat below that achieved by selective accentuation of the hexosemonophosphate shunt. This suggested that the rate of cholesterol formation was governed by the relative amounts of glucose available for distribution to the oxidative pathways: the pgo pathway tending to increase cholesterol synthesis, and Embden-Meyerhof glycolysis tending to suppress it.

The pgo pathway is dependent on the oxidation of glucose-6-phosphate to phosphoglucuronate, which is the major source of reduced TPN. This oxidative process is catalyzed by both glucose-6-phosphate dehydrogenase and phospho-

gluconic acid dehydrogenase. In diabetes, these enzymes are diminished in quantity in the liver, thereby retarding the hexosemonophosphate shunt (60). *In vitro*, these deficiencies are not corrected by insulin, but the concentrations of both enzymes are doubled by the administration of thyroxin to diabetic rat liver (60). As a result of insulin deficiency, glucose available for metabolism within the cell is markedly reduced, especially that portion utilized by the PGO pathway. Consequently, lipogenesis from acetyl CoA is limited by the availability of TPNH_2 formed in the hexosemonophosphate shunt. This has been confirmed by studies with diabetic rat liver homogenates, where the addition of TPN restored an essentially normal rate of fatty acid and cholesterol synthesis by provocation of the PGO pathway (64).

Another source of TPNH_2 is the TCA cycle. This cycle is restrained in diabetes as glucose conversion to pyruvate is retarded (1, 2, 6-8, 15, 17, 18, 30, 60, 65, 66). Since production of oxalacetic acid is consequently impaired, less of the available acetyl CoA can condense with it to form citrate. As a result, TPNH_2 production via isocitric dehydrogenase is reduced. The importance of this failure is further emphasized by the observation of Brady *et al* that the addition of citrate to diabetic rat liver extracts stimulates lipogenesis (59).

As TPNH_2 deficiency impairs the reduction of crotonyl CoA to butyryl CoA, fatty acid synthesis is halted at the 4-carbon stage, evoking an accumulation of ketone bodies. With acetyl CoA utilization reduced, the acetate pool in the liver expands, and forces the normal equilibrium of acetoacetyl CoA breakdown to shift from further acetate formation to more rapid deacylation to form excessive quantities of ketone acids. Although one might suspect that pyruvate, oxalacetate, or a TCA cycle intermediate would correct the defect in acetate utilization, Bessman has shown that treatment of diabetic coma with succinate alone is ineffective (65). It appears, then, that conversion to glucose-6-phosphate requires a phosphate acceptor, which is available only in the presence of insulin.

Effect on Fat Oxidation

While fatty acid synthesis lies relatively dormant, fatty acid oxidation persists at an accelerated rate (7, 12, 17, 19, 22-24, 30, 66). In spite of reduced TCA cycle activity, the oxidation of any of its components, in the liver and kidney at least, can initiate the oxidation of approximately 15 moles of fatty acid (2). Apparently, fatty acid oxidation proceeds along a different pathway from fatty acid synthesis, since reversal of the crotonyl CoA→butyryl CoA reaction requires flavin adenine dinucleotide (FAD), rather than TPNH_2 (8, 21).

Effect on Fat Depots

The effect of inadequate carbohydrate utilization on adipose tissue has also been recognized, resulting in an increased output of fatty acids from storage (11, 12, 29, 30, 53). NEFA are released in greatly elevated amounts, along with triglycerides (11, 14, 31, 67-69), and adipose uptake of NEFA is concurrently blocked (30). This provides additional fatty acid substrate to the liver for conversion to ketone acids (11, 14).

The response of NEFA in normal animals to a variety of stimuli has been studied independently by several investigators. NEFA levels have been shown to fall under conditions which favor increased glucose utilization for fat synthesis in adipose tissue (10, 11, 29, 30), apparently as a result of the diminished rate of liberation of NEFA from adipose tissue, not because of an augmented rate of removal of NEFA from the circulation (29, 30). This drop in circulating NEFA concentration is seen following administration of insulin (11, 29, 30, 36, 70), glucose (10, 11, 29, 30, 36, 70), glucagon, tolbutamide (29, 30), dibenamine, and hexamethonium (71). A rise in circulating NEFA is seen under conditions promoting the mobilization of fat from storage, such as diabetes mellitus, fasting (11, 70), administration of epinephrine (11, 30, 34, 36, 70), as well as norepinephrine, growth hormone, or ACTH (30), and cortisone (72). Psychic stress has also been noted to produce an increase in blood NEFA levels (30), and results with fat feeding have been variable (10, 30, 70).

The ability of epinephrine to elicit elaboration of NEFA from adipose tissue *in vivo* appears to be dependent on adequate thyroid activity. Goodman and Knobil were able to abolish this epinephrine-stimulated NEFA mobilization in the rhesus monkey by hypophysectomy, despite the persistence of hyperglycemia (73). Significant NEFA response in these animals was restored by the administration of thyrotropin or triiodothyronine, but was not influenced by treatment with hydrocortisone, ACTH, growth hormone, or prolactin.

SUMMARY

The inability of the body to handle carbohydrate at a normal rate in diabetes mellitus has a profound effect on fat metabolism. Glucose phosphorylation appears to be impaired by a deficiency in reduced TPK to the severe detriment of fatty acid synthesis. The inadequacy of this substance, which catalyzes the reduction of crotonyl CoA to butyryl CoA, has been attributed principally to a striking retardation in glucose oxidation via the phosphogluconate oxidative pathway, and, to a less significant degree, via isocitric dehydrogenase in the tricarboxylic acid cycle. A reduction in the hepatic concentration of glucose-6-phosphate dehydrogenase and phosphogluconic acid dehydrogenase has been demonstrated in the diabetic rat, and has been implicated in the impairment of oxidation of glucose-6-phosphate to phosphogluconate in the hexosemonophosphate shunt. The retardation of pyruvate formation from glucose diminishes oxalacetate production, thereby restricting TCA cycle activity. However, fatty acid mobilization from adipose tissue accelerates markedly. This combination of circumstances presents the liver with an excessive load of fatty acid substrate, which can be degraded only to the 4-carbon stage, and shunted heavily in the direction of deacylation to manufacture an overabundance of ketone bodies, with the ultimate production of ketosis.

DIABETIC HYPERLIPEMIA

As a result of the impaired carbohydrate metabolism in diabetes, the diabetic animal subsists largely on fat. Owing to the disturbance of fat metabolism, fatty

acids are rapidly mobilized from fat depots (5, 30, 31, 53, 74), thereby causing an elevation of the serum lipid level, which is probably accentuated by a factor of hemoconcentration (31, 74). This sharp rise in serum total lipid content affects all lipid fractions: triglycerides, to the greatest extent, and, in order of decreasing response, phospholipids, free cholesterol, and cholesterol esters (31, 74). Such hyperlipemia, due to the excessive elaboration of fat from depots, is called "transport hyperlipemia" (75), although a smaller portion of the serum rise may be attributed to delayed removal of lipid from the circulation (5, 74). Triglycerides are the first lipid fraction to be affected by lack of diabetic control (67), and probably stimulate the liver to elaborate larger quantities of β -lipoprotein, which, in turn, provokes a rise in serum phospholipids and cholesterol (53). Because of the predominance of neutral fat, the serum may appear lactescent (31, 74).

Treatment of diabetic acidosis with insulin and glucose restores an adequate rate of carbohydrate metabolism and corrects hemoconcentration, thereby producing a fairly rapid fall of serum lipid levels to normal (74). The almost immediate disappearance of excessive serum NEFA after insulin therapy suggests that NEFA may exert a major influence on the subsequent decline of plasma triglycerides (31).

The mechanism of action of insulin on the disturbed fat metabolism in diabetes has not been thoroughly clarified. Some investigators postulate a direct action on adipose tissue to accelerate lipogenesis, based on the contrasting effects of epinephrine, on the one hand, and glucose or insulin, on the other, on the rate of evolution of NEFA (36, 72). Other workers suggest a direct action on the liver to enhance carbohydrate utilization, with a secondary restriction of fatty acid breakdown. Lossow *et al* inferred this from studies with labeled palmitic and octanoic acids in diabetic rats (20). Haft and Miller found insulin to be ineffective *in vitro* in restoring lipogenesis and carbohydrate balance in diabetic rat liver slices, but effective *in vivo* or when added to isolated, perfused diabetic livers from donor rats in mild or moderate ketosis (18). Gillman *et al* postulate that diabetic ketonemia, hyperglycemia, and hyperlipemia can be dissociated. They have demonstrated that hypophysectomy in pancreatectomized baboons with untreated diabetes markedly ameliorates the disorder of fat metabolism, with disappearance of ketonemia, while failing to correct the impairment of carbohydrate metabolism. If cortisone, alone, or with thyroxin, is then administered, the lipemia increases, but ketonemia does not reappear (75).

IDIOPATHIC HYPERLIPEMIA

Biochemical Alterations

Hyperlipemia signifies an elevation of total blood lipids to a level beyond 1 Gm per 100 cc plasma, owing principally to a significant rise (greater than 400 mgm %) in triglyceride concentration (69, 75). Triglyceride content is represented as the difference between total fatty acids and the sum of fatty acids esterified with cholesterol or combined in phospholipids (31). When serum neutral fat exceeds 590 mgm per cent or 20 mEq/L (54, 77), or is increased by 50–150 per cent above normal (75), the serum appears lactescent. Holt also ascribes

lactescence to particle size, relative bile salt and phospholipid concentrations, and lipoprotein combinations (78). Studies of lipoproteins in idiopathic hyperlipemia have shown an elevation in all S_f classes (79).

Idiopathic hyperlipemia has been classified by Thamhauser as a "retention hyperlipemia," since both clearance of circulating lipids and deposition from capillaries into the fat depots are delayed (75). This concept was confirmed by Lever and Waddell in 1955 by demonstrating delayed transport of intravenously-administered emulsified neutral fat in patients with the disorder, while emulsifying agents alone had no effect on serum lipids (80). Turner corroborated this further by measuring rates of removal from the circulation of oral I^{131} -triolein in normal and hyperlipemic individuals (58).

The reasons for this retardation in lipid clearance is poorly understood. In some patients with idiopathic hyperlipemia, lipoprotein lipase has been found to be absent (81) or inhibited (82). Conner and Armstrong, however, refute both of these observations by measuring lipoprotein lipase activity in post-heparin plasma over a 24-hour period in normals and in patients with hyperlipemia, either idiopathic or secondary to nephrosis or hypothyroidism, given an injection of heparin. LPL activity was adequate in all, once albumin was added to the plasma of the nephrotic (83).

A plasma fraction in normal humans has been isolated, which is capable of inhibiting the heparin clearing reaction of lipemic plasma (84, 85). This appeared to Hollett and Meng to be a glycoprotein, measurable as glucosamine. It was inferred that the mechanism of inhibition is by means of alteration of the physical state of the fat substrate, since incubation of the active plasma fraction with fat emulsion produced an increase in the optical density of the system, as well as an observable enlargement of fat particles (85). Mitchell recently ascribed the inhibitory activity to a substance produced by platelets (86). This was based on the less rapid clearing of lipemic plasma when large quantities of platelets were present. Moreover, a cell-free platelet extract is capable of inhibiting the clearing of lipemic plasma and fat emulsions, even in the presence of pancreatic lipase. A lipid-mobilizing hormone has also been found in plasma, which is capable of inducing the release of triglycerides from adipose depots (87). It is apparently stored or produced in the posterior pituitary gland, and its action is inhibited by depolymerized hyaluronic acid. Its relation to idiopathic hyperlipemia is not yet fully clarified.

The Pancreas and Hyperlipemia

Owing to the frequent association of chronic relapsing pancreatitis with idiopathic hyperlipemia, the relationship between the pancreas and fat metabolism has long been an area of investigation. An acceptable clarification has not yet evolved with respect to which condition is the predecessor, and which, the successor.

Hyperlipemia may be divided into transient states which accompany isolated acute episodes of pancreatitis and persistent states, of familial or non-familial nature, associated with relapsing pancreatitis.

The mechanism by which serum lipids may be elevated during acute attacks of pancreatitis remains obscure. Moreover, in patients with repetitive pancreatic insults, even with an unlimited fat intake, hyperlipemia and its associated clinical manifestations are absent during the quiescent intervals (88).

In idiopathic hyperlipemia, recurrent bouts of acute abdominal pain are common, although by no means universal (69, 75, 88-93). The origin of the pain is often obscure. Since a reduction in the serum lipids frequently occurs during or immediately following the abdominal episode (91), and is often accompanied by hepatic and splenic enlargement, these crises were originally attributed to rapid hepatic accumulation of lipid (69). This interpretation has been virtually abandoned since the advent of liver biopsy techniques, which fail to reveal the presence of fatty infiltration or foam cells in the liver in almost all instances (91).

The possible importance of transient lymphatic obstruction in the etiology of abdominal crises gained prominence with reports of a long-term study by Ahrens of a young patient with recurrent abdominal pain and documented hyperlipemia since the age of five (94). Surgical exploration 21 years later, during an acute episode, disclosed lacteal distension and chylous ascites, with a grossly normal pancreas, liver, gall bladder, and spleen. A retroperitoneal mass was visualized, but not investigated further. The pathogenetic explanation forwarded is one of periodic, temporary thoracic duct obstruction, with consequent chylous exudation into the peritoneal cavity, retroperitoneal tissues, and mesenteric root, resulting in tissue distension and abdominal pain. Serum lipids would then decline, aided by the low fat intake imposed by anorexia.

The diagnosis of relapsing pancreatitis was suggested not only by the clinical picture, but also by the lipid changes accompanying experimental pancreatitis (95, 96), and has been confirmed in many patients by serum and urinary pancreatic enzyme determinations (91, 92), as well as by exploratory laparotomy (92). It is presumed, therefore, with apparent justification, that the characteristic relapsing abdominal colic usually represents acute exacerbations of pancreatitis (75, 78, 91).

Chronic pancreatitis may also go unrecognized in idiopathic hyperlipemia (75, 78, 91). Bartholomew and Comfort have reported chronic pancreatitis without abdominal pain, diagnosed by the presence of pancreatic calcification on roentgenography, with or without associated diabetes mellitus or steatorrhea, by an abnormal pancreatic secretory response following the administration of secretin, or by surgical exploration (97). Since in these instances lactescent serum is usually the initial clinical finding, the difficulty in establishing pathogenesis becomes instantly apparent.

Pathogenesis of Idiopathic Hyperlipemia with Relapsing Pancreatitis

Since diabetes mellitus is often associated with pancreatitis, it is logical to consider the elevation in serum lipid level to be possibly related to the diabetes. Gardner and Fawcett noted moderately severe diabetes in two patients with acute pancreatitis and hyperlipemia, in whom serum lipid levels were restored

to normal within two weeks by dietary fat restriction and insulin therapy (98). Most investigators, however, believe that the disturbance in carbohydrate metabolism is usually of insufficient magnitude to provoke a hyperlipemic response (88, 91, 96).

In insulin-treated, pancreatectomized dogs, Dragstedt and his associates demonstrated the gradual development of hyperlipemia, over a period of weeks, when small amounts of pancreatic juice were introduced into the intestinal tract (99). This intestinal pancreatic activity was derived from a small remnant of pancreas with diversion of its external secretion to the intestine or from ingestion of raw pancreas. However, elaboration of pancreatic enzymes into the circulation was prevented by the pancreatectomy. When pancreatic substances were excluded from the intestinal tract entirely, serum lipids fell. At first, these observations were heralded as evidence for the existence of an internal (hormonal) pancreatic secretion—lipocaic—capable of regulating serum lipids by preventing their accumulation in the blood stream (75, 99). The absence of lipocaic would, therefore, permit hyperlipemia to appear when the absorptive capacity of the alimentary tract was intact.

The slow rise in serum lipids attributed to a deficiency of lipocaic fails to correlate with observations that experimental pancreatic trauma rapidly gives rise to hyperlipemia unless the reduction in lipocaic were to precede the onset of acute pancreatitis (96). The evidence that chronic pancreatic insufficiency and the latent intervals between recurrent attacks of acute pancreatitis are not associated with hyperlipemia (88, 91), together with the failure of hyperlipemia to respond to orally- (100) or intravenously-administered pancreatic extract (75), casts serious doubt as to the validity of the hormonal concept.

Since lipocaic has never been isolated, and since raw pancreas ingested orally can induce hyperlipemia and lipotropic activity in fatty livers in depancreatized dogs maintained on insulin, Chaikoff and his collaborators insist that the lipid regulatory factor in pancreas is in the external secretion, rather than the internal, as implied by Dragstedt (101-104). This enzyme (? trypsin) appears to act in the intestinal tract, possibly by stimulating the absorption of bound methionine and choline from the diet.

The influence of unsaturated fatty acids in the diet on serum lipid concentration has been frequently stressed. A diet high in unsaturated, or essential, fatty acids (vegetable fat) significantly lowers cholesterol and, to a lesser degree, phospholipid levels in the serum (105-109). Their mechanism of action may be focused on increasing the efficiency of fatty acid transport (109). Since unsaturated fatty acids require pancreatic juice for optimal absorption from the intestinal tract, it has been suggested that pancreatitis, with its associated deficit in pancreatic secretion, may induce hyperlipemia by precluding adequate absorption of these fatty acids (110). The absence of hyperlipemia in chronic pancreatic insufficiency mitigates strongly against this hypothesis, as does the demonstration by Ahrens and his group that maintenance of the normal serum lipid concentration (all fractions) is not dependent on the presence of dietary unsaturated fatty acids (111).

The ability of glucagon to correct alimentary hyperlipemia is well established (29, 30, 95, 96). Destruction of the pancreatic alpha cells by cobaltous chloride (95) or by instillation of a potent staphylococcal toxin into the ligated pancreatic duct of dogs and rabbits (96) impairs glucagon production, causing serum lipids (particularly triglycerides) gradually to rise, with the ultimate development of lactescent serum. Albrink and Klatskin reject this effect as a likely source of hyperlipemia in acute pancreatitis, because of an apparent discrepancy in the rate of appearance of lipid response experimentally and clinically, the latter being the more rapid (88). Wang, Strauss, and Adlersberg, however, observed a rapid accumulation of lipids in serum one to four days after the production of pancreatic injury (96).

The role of calcium metabolism in pancreatitis is not yet clarified. Marked calcium deposition has been discovered in necrotic pancreatic and adipose tissue of patients with acute pancreatic necrosis without hyperlipemia (112). Presumably, the calcium was incorporated into soaps by the liberated fatty acids, and maintained in solution by neutral fat. This shift in calcium distribution apparently depleted serum calcium to subnormal levels (7-8.8 mgm per cent), with the production of hypocalcemic tetany, responsive to the intravenous administration of calcium salts. Tetany was also observed in two patients with acute pancreatitis and secondary hyperlipemia, whose serum calcium and pH values were normal (113). In these patients, tetany was unresponsive to parenteral calcium, but improved with the administration of parathyroid hormone or subsided spontaneously with the progressive decline in serum lipid levels. These latter cases suggest that NEFA may have preferentially combined with calcium, instead of albumin, with a consequent retardation in triglyceride clearance and reduction in serum ionizable calcium, thereby provoking hyperlipemia and normocalcemic tetany.

Liquefaction of fat has been visualized at the site of necrotic pancreatic and adipose tissue in acute pancreatitis (112, 114). It has, therefore, been postulated that blood vessel walls, damaged locally by pancreatic enzyme activity, permit entry of the digested interlobular and peripancreatic fat into the circulation. This probably enters in liquid form, since triglycerides and fatty acids, such as oleic acid, are fluid at body temperature (112). Once in circulation, fat embolism may occur, especially to the kidney and lung (88, 112, 114), but also in widely disseminated form (91). Since triglycerides have the same staining properties as the lipid found in areas of fat necrosis and in fat emboli, it has been inferred that adipose tissue injury is the probable origin of fat for embolization, rather than the free fatty acids released (88). This sequence of events has been considered as a possible explanation for the frequency with which fat embolism is seen in chronic alcoholics (115). Klatskin and Gordon noted sufficient elevation of pancreatic enzyme activity in some attacks of acute pancreatitis to produce *in vitro* clumping of chylomicra (91).

Fat embolization has often been attributed to a predisposition of blood to coagulate in the presence of hyperlipemia. Studies in alimentary hyperlipemia have repeatedly shown rapid clotting time of blood in silicone-coated tubes (116, 117), as well as shortened one-stage prothrombin times, utilizing Russell viper-

venom (stypven) as a fat-free thromboplastin (117, 118). These findings were later corroborated by Robinson and Poole who observed a marked increase in thrombin generation following the addition of rat chylomiera or one of several brain ethanolamine phosphatide preparations to plasma freed of particulate fat (119). Since ionophoresis and chromatography disclosed the presence of an ethanolamine-like component in acid hydrolyzates of chyle, they concluded that chylomiera probably potentiate rapid blood coagulation by the action of ethanolamine phosphatide.

Whether fat embolism is a result or a cause of pancreatitis in idiopathic hyperlipemia remains a matter of speculation, since hyperlipemia of any origin, primary or secondary, may be accompanied by fat embolization. Hyperlipemia could conceivably instigate pancreatitis by producing xanthomatous lesions in the pancreas, which might undergo spontaneous resolution by dietary fat restriction, and thereby escape pathologic detection. Or, perhaps, atherosclerotic plaques are formed in the pancreatic blood vessels which are capable of inducing an ischemic form of pancreatitis (91). This would seem unlikely, since neither the symptoms nor the histologic findings is consistent with a course of chronic arterial insufficiency.

In summary, it appears that acute pancreatitis may produce transient secondary hyperlipemia by a mechanism not well clarified at the present time. Several mechanisms are currently under scrutiny. Post-mortem studies in both human and experimentally-produced pancreatitis have revealed liquefaction of fat in necrotic adipose and pancreatic tissue, which may cross locally injured vascular walls, thereby elevating serum lipid levels to an abnormal range. Experimental destruction of pancreatic alpha cells may have a clinical counterpart, by which glucagon deficiency may interfere sufficiently with carbohydrate metabolism to produce hyperlipemia. Recent observations in patients with acute pancreatitis and hyperlipemia with concomitant tetany have suggested the possibility that both the rise in serum lipids and the clinical tetany may be the result of triglyceride binding with ionized calcium, rather than albumin, consequently reducing the efficiency of lipid transport.

In idiopathic hyperlipemia with relapsing pancreatitis, serum lipid values are always above normal, owing to a delay in lipid transport by unknown factors. In some instances, this delay appears to be related to a deficiency in lipoprotein lipase or, perhaps, to an excessive elaboration of a lipid-mobilizing hormone by the posterior pituitary gland. Since chronic pancreatitis may exist in an asymptomatic form, it is difficult to outline the proper sequence of alterations. Hyperlipemia probably precedes the development of pancreatic disease, since lipid abnormalities may be familial in many instances, suggesting an inborn error of metabolism (88, 120, 121). In addition, hyperlipemia may exist without any clinical evidence of pancreatitis, or may persist long after abdominal crises appear to have ceased (91). Cutaneous xanthomata may precede abdominal pain in an acute exacerbation, and both skin and abdominal symptoms may be at least partially controlled by regulation of serum lipid levels (88, 91). The suggested mechanisms by which idiopathic hyperlipemia may produce pancreatitis include

fat embolism or the production of xanthomatous or atherosclerotic lesions in the pancreas.

CLINICAL MANIFESTATIONS

The clinical syndrome of idiopathic hyperlipemia with relapsing pancreatitis is usually first manifest in childhood or early adult life, and appears predominantly in male Caucasians (90). A family history is present in a small proportion of the cases (88, 91, 104, 121, 122). Hyperlipemia is sustained in the intervals between abdominal crises. During crises, serum lactescence is frequently observed, and may be accompanied by cutaneous xanthomata and lipemia retinalis (69, 75, 88, 89, 90, 91, 92, 120). The xanthomata are usually eruptive, appearing first on extensor surfaces as yellow papules with inflammatory halos, and later becoming more diffuse (90). Xanthoma tuberosum is considerably more common than either xanthoma tendinosum or xanthelasma, in contrast to a reversed frequency seen in idiopathic hypercholesteremia (89). In lipemia retinalis, the retinal arteries and veins both appear salmon pink in color, with the latter sometimes containing a visible stream of fat droplets (90).

Hepatic or splenic enlargement may occur only during the acute episode or may be persistent (69, 75, 90, 92), may remain absent (121), or may not appear until hyperlipemia is long-standing (75).

A predisposition to atherosclerosis is apparent, with 34 per cent of Adlersberg's series manifesting coronary artery disease (89). Engelberg has attempted to correlate serum levels of cholesterol and low-density lipoproteins with abnormalities on ballistocardiography (123). The resting ballistocardiogram showed a tendency, most prominent below the age of fifty, for abnormalities to be associated with higher lipid values. A better correlation with serum lipids, at all ages, was observed with exercise, higher lipid levels being found when exercise intensified the ballistocardiographic abnormality and lower levels noted when the record improved after exercise.

In idiopathic hyperlipemia, transient cerebral manifestations were noted in 4.5 per cent and diabetes mellitus was found in 7 per cent of 48 patients (89). When idiopathic hyperlipemia, diabetes, and severe vascular disease coexisted, Adlersberg and Wang felt this constituted a separate clinical syndrome (120). This group of patients differed from those without diabetes by exhibiting a marked lability in the serum lipids, as well as aggravation of the underlying hyperlipemia by lack of diabetic control, even in the absence of ketosis (124). Treatment of both the diabetes and the hyperlipemia rarely brought the total lipid values to normal. In contrast, uncontrolled diabetes with secondary hyperlipemia is accompanied by ketosis, and generally produces a much less significant rise in serum lipids, which can be restored to normal by proper diabetic management alone.

Familial hyperlipemia is regarded by Wilkinson as a genetic predisposition, inherited as an incomplete dominant trait with little penetrance (122). Homozygosis produces both hyperlipemia and other clinical abnormalities, whereas the heterozygous state yields an individual with the lipid metabolic defect alone.

TREATMENT

Many therapeutic modalities have been utilized in an endeavor to regulate serum lipid levels. When control is achieved, even without quite reaching the normal range, many of the clinical manifestations will be arrested or held in abeyance for a duration of time exceeding the pretreatment course.

Rigid dietary restriction of fat, cholesterol, and calories has been successful in clearing serum lactescence by lowering serum lipids (75, 88, 91, 120). Selective limitation of dairy foods, coconut oil, and alcohol, however, has been reported to maintain a normal serum lipid concentration (125). Wilkinson prefers a regimen of spaced fat feeding, allowing postprandial hyperlipemia to subside prior to the next meal. This occurs within 24 hours in 75 per cent of his patients. Spacing of meals is gauged by the time required for an individual to clear his serum of a fat load after one or more months of equilibration (122). Intravenous neutral fat emulsion will decrease serum triglycerides and cholesterol, but is impractical for long-term maintenance therapy (80).

Administration of lecithin, choline, thyroxine, insulin, and liver extract (100), as well as blood transfusions (75, 100), is ineffective. Estrogen therapy combined with a low-fat diet, given for at least two months, will partially control serum lipids (126, 127). β -sitosterol interferes with cholesterol absorption from the gut and from bile, probably by competition with cholesterol for esterification. When given orally to patients with idiopathic hyperlipemia, a prolonged fall in serum cholesterol, triglycerides, and total lipids is only moderately well obtained, the effect on phospholipids being less marked (128). The use of oral chlorpromazine in dosages of 100–200 mgm daily has, in two patients, convincingly lowered all serum lipid fractions, particularly triglycerides, to near-normal levels, with a subsequent rise to the pretreatment range upon discontinuance of the drug (129).

The striking effect of heparin on acceleration of fat transport has stimulated extensive clinical trials in idiopathic hyperlipemia. A single injection of heparin causes a fall in all lipid components (129–131), as well as a shift in lipoproteins to the lower S_f classes (79). A continuous intravenous infusion in alimentary hyperlipemia returns the abnormal I^{131} -lipid tolerance curve to normal (58). One to two thousand I.U. of sublingual heparin clarifies postprandial hyperlipemic serum (132). Although sustained normal lipid levels are seldom obtained, heparin therapy represents an important adjunct to dietary management. Its usefulness will increase as the simpler routes of administration prove their merit with more protracted evaluation.

Observations by Altschul and his associates (133), later confirmed by others (134–137) indicated that nicotinic acid, in contrast to its amide, is a potent agent in depressing serum cholesterol levels in normal and hypercholesteremic individuals. Its mechanism of action is unknown. Application of nicotinic acid to patients with idiopathic hyperlipemia, in daily oral dosages of 3 Gm, maintained reduction of all serum lipid fractions, with cholesterol, triglyceride, and total lipid response exceeding that of phospholipids. Carbohydrate tolerance in non-diabetic individuals was also consistently and significantly diminished (138). As yet, no major side-effects have been reported.

Management of patients with idiopathic hyperlipemia is still imperfect. Dietary fat, cholesterol, and calorie restriction appears to be important. The supplementary administration of nicotinic acid, heparin, or ethinyl estradiol seems to enhance the effectiveness of dietary therapy, but frequently does not achieve the optimal sustained depression of serum lipids to normal levels.

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FAMILIAL DEFECT IN LIPID METABOLISM MASKED BY DIABETIC HYPERLIPEMIA

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INTRODUCTION

Biochemical abnormalities in lipid metabolism may occur in response to disorders of biliary, pancreatic, endocrine, or renal function. When the serum total lipid level exceeds 1 Gm per cent, and the predominant rise is in the triglyceride (neutral fat) fraction, serum lactescence may appear, and the resultant state is called hyperlipemia. When hyperlipemia is unassociated with any known causative factor, it is designated idiopathic, and represents a primary, inborn defect in circulating lipid clearance, whereby lipids are retained in the blood stream for grossly prolonged periods of time (1-3).

Idiopathic hyperlipemia is a familial condition apparently inherited as an incomplete dominant trait (4, 5). Some patients with this disorder have been found to be deficient in a specific tissue enzyme, lipoprotein lipase, which, when activated by heparin, is capable of accelerating the clearance of circulating lipids (6, 7). The recovery in plasma of a lipid mobilizing hormone released by the posterior pituitary gland has led to speculation that it may be present in excessive amounts in the hyperlipemic state (8, 9). Its mechanism of action is to stimulate the elaboration of triglycerides from adipose tissue into the circulation.

The carbohydrate metabolic defect in diabetes mellitus is accompanied by a retardation of fatty acid synthesis, accelerated ketogenesis, and excessive lipid mobilization from fat depots. When diabetes is uncontrolled, ketosis and hyperlipemia may result (1, 10-13). The biochemical deviations from normal fat metabolism in diabetes mellitus and idiopathic hyperlipemia, and the accompanying clinical characteristics, have recently been reviewed extensively (14).

When lactescent serum is found in a patient with uncontrolled diabetes mellitus, its origin is often difficult to discern, since it may reflect the presence of either diabetic hyperlipemia or idiopathic hyperlipemia or both. Although the principal immediate concern is the rapid regulation of the diabetic ketosis, the long-term management and prognosis depend heavily on the early recognition of an underlying lipid metabolic abnormality if one exists. To illustrate this problem, the following patient with idiopathic hyperlipemia, complicated by diabetic ketosis is presented.

CASE REPORT

A 41 year-old white, American male diabetic entered The Mount Sinai Hospital because of diabetic ketosis and lactescent serum. The patient, a former prize-fighter, was known to have had diabetes mellitus of five years duration, controlled for the first four years by daily injections of 15 units of globin insulin, supplanted during the last year by 250 mgm

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TABLE I

Serial Lipid Determinations of the Patient's Fasting Serum, with Random Lipid Partition Studies of Fasting Serum from the Patient's Parents

Serum Analyzed	Date	Gross Appearance	Total Lipids (mgm %)	Phospholipids (mgm %)	Total Cholesterol (mgm %)	Cholesterol Esters (mgm %)	Triglycerides (mgm %)	Fasting Blood Sugar (mgm %)	Glycosuria (Clintest)	Ketonuria
Patient	7-22-58	Lactescent	10,530	1,040	1,108	660	8,382	224	Variable	Present
Patient	7-26-58	Turbid	2,555	464	526	368	1,565	188	Variable	Absent
Patient	3-9-59	Slightly lactescent	2,620	436	462	289	1,722	167	34%	Absent
Patient's Mother	7-26-58	Turbid	1,605	400	367	265	838		None	Absent
Patient's Father	8-1-58	Clear	925	260	219	168	497		None	Absent

of tolbutamide each day. For several months, the patient had noted the presence of 2 to 4 plus glycosuria, as determined by clintest tablets. He related a two-month history of virtually constant, dull, pulsatile, occipital headaches, most severe around midnight, associated with polyuria, polydipsia, weakness, paresthesias of the right hand, and a papular skin eruption on the anterior thorax and lower extremities, which on occasion was pruritic. During the past month, the patient was aware of frequent flatulence and postprandial retrosternal burning, unrelieved by antacids, as well as mild recurrent calf pain on walking and infrequent palpitations of the heart. The patient's appetite was excellent, and his weight had remained stable. He denied any acute episode of abdominal pain in the past, diarrhea, previous exanthema, dyspnea, or anginal-type pain.

More than 20 years earlier, the patient had been treated for pneumonia and two cerebral concussions. Fifteen years previously, he contracted falciparum malaria in New Guinea, accompanied by alopecia universalis. Adequate atabrine therapy was administered, with no subsequent adverse sequelae. There was no knowledge of persistent splenomegaly.

The patient's mother is a known diabetic with coexistent idiopathic hyperlipemia. Under optimal diabetic control, her total serum lipids measured 1,605 mgm per cent, of which 52 per cent (838 mgm per cent) were triglycerides, the remaining lipid fractions also being elevated. The patient's father is a non-diabetic with essentially normal serum lipids in all fractions. His total lipid concentration was 925 mgm per cent, containing 53 per cent (497 mgm per cent) triglycerides (Table I).

The patient on physical examination appeared husky and somewhat obese. He was afebrile, with a ventricular rate of 80, and a blood pressure of 120/75. Generalized alopecia was evident. A skin eruption was present on the anterior chest and legs, consisting of small, discrete, non-pustular, yellow papules with a red base. Funduscopic changes consistent with lipemia retinalis were observed in the absence of other retinal abnormalities. There was firm, non-tender hepatic and splenic enlargement, with the liver and spleen descending four cm and two cm beneath the right and left costal margins, respectively. Peripheral pulses were full. The only neurologic abnormality was a diminished vibratory sensation in the feet and ankles. The heart was slightly enlarged, with a normal third heart sound audible along the left sternal border. There was also moderate benign hypertrophy of the prostate.

At the time of admission, the patient's urine contained glucose in excess of two per cent, in association with ketone bodies. The blood was grossly creamy, and fasting blood sugar determinations ranged between 188 and 262 mgm per cent. Serum amylase was ten modified Somogyi units (normally 80-180). An erythrocyte sedimentation rate was 24 mm in one hour.

Serum sodium and chloride concentrations were markedly depressed while lactescence persisted (probably artifactual), but subsequently, the electrolyte levels returned to normal. The carbon dioxide content of the venous blood was 23.4 mEq/L. Thyroidal radioactive iodine uptake was 35 per cent of the administered dose in 24 hours. The electrocardiogram showed nonspecific ST segment and T wave changes. Abdominal roentgen films failed to disclose the presence of calcifications in the region of the pancreas. Serum protein studies revealed a mucoprotein level of 111 mgm per cent (normally 48-75), acid-precipitable globulin of 19.5 units (normally 4-8), and a zinc sulfate turbidity of four units (normally 4-8). This was interpreted to indicate high α_1 globulin and α_2 plus β -globulins, with a relatively low gamma globulin, a combination compatible with hyperlipoproteinemia.

Total serum lipids were 10,530 mgm per cent, with 8,382 mgm per cent triglycerides, 1,040 mgm per cent phospholipids, and 1,108 mgm per cent cholesterol, of which 660 mgm per cent was esterified (Table 1).

The patient was immediately started on 65 to 75 units of NPH insulin daily and a low fat, low calorie diet. After three days had elapsed, the ketosis had subsided, but varying quantities of glycosuria persisted. By this time, fasting serum lipid values had declined to a total concentration of 2,555 mgm per cent of which 1,565 mgm per cent represented triglycerides, 464 mgm per cent phospholipids, and 526 mgm per cent cholesterol, with 368 mgm per cent cholesterol esters. Within a few more days, the eruptive xanthomata and lipemia retinalis had disappeared, and the liver had receded somewhat in size. By the twelfth day, the patient was aglycosuric, and left the hospital against advice.

Seven and one-half months later, after continued diabetic therapy, the patient's serum again appeared lactescent. At this time, a fasting blood sugar level was 167 mgm per cent, associated with considerable glycosuria and no ketonuria. Total serum lipids were 2,620 mgm per cent, containing 1,722 mgm per cent triglycerides, 436 mgm per cent phospholipids, and 462 mgm per cent cholesterol, of which 289 mgm per cent was esterified (Table 1).

DISCUSSION

The combination of historical features, physical findings, and therapeutic response to a diabetic regimen serves to differentiate diabetic from idiopathic hyperlipemia. In diabetes mellitus, lactescent serum is seen only in the presence of hyperglycemia and ketosis, with rare exceptions, and usually without any characteristic changes in physical appearance. Hepatomegaly may be present, however, but its onset does not typically coincide with the development of hyperlipemia. Following adequate treatment of the diabetic ketosis, the serum lipid levels return fairly rapidly to normal as the ketonemia disappears (10, 12). Although diabetes frequently is familial, diabetic hyperlipemia is not present in well regulated diabetic relatives.

In contrast to the diabetic with secondary hyperlipemia, the patient with idiopathic hyperlipemia may have a preceding history of serum lactescence. There is occasionally a familial incidence of hyperlipemia. Frequently, the patient describes recurrent attacks of acute abdominal pain, which usually represent a chronic, relapsing pancreatitis (1, 4, 15, 16). Often there is hepatic and splenic enlargement (17, 18), eruptive xanthomatosis (18, 19), and lipemia retinalis (18). Not infrequently, xanthoma tuberosum is present (15). When the serum lipid level in idiopathic hyperlipemia is augmented by diabetic hyperlipemia, the latter component usually responds well to insulin therapy. However, serum lipid levels (all fractions) remain somewhat elevated, even with dietary fat restriction.

When idiopathic hyperlipemia is accompanied by diabetes mellitus and severe vascular disease, the serum lipid level fluctuates widely, and may be markedly exaggerated by lack of diabetic control, even without ketosis. Treatment of the hyperlipemia in these patients is generally unsatisfactory. The different behavior of these individuals led Adlersberg and Wang to classify this combination of findings as a distinct syndrome (20).

Although appropriate regulation of diabetes mellitus may minimize the incidence of premature atherosclerosis, if idiopathic hyperlipemia in the same patient remains untreated, the same predisposition to coronary heart disease exists (15). Chiefly for this reason, correction of the primary lipid defect must be attempted. Although maintenance of a normal serum lipid level is seldom achieved, the most favorable response follows the institution of a low fat, low calorie diet, supplemented by an antilipemic drug, particularly heparin (21-23), nicotinic acid (24, 25), or ethinyl estradiol (26).

The patient described emphasizes the difficulty in evaluating hyperlipemia in a diabetic. Lactescent serum remained undiscovered until lack of diabetic control imposed an additional embarrassment on the already abnormal fat metabolism. As serum lipids rose to remarkable heights, there appeared the typical clinical manifestations of hyperlipemia: eruptive xanthomatosis, lipemia retinalis, and hepatosplenomegaly. (The role that the previous malaria played in the current enlargement of the spleen is undetermined). Relapsing pancreatitis is not an essential feature for diagnostic confirmation. In spite of the low serum amylase determination, there is no clinical evidence in this patient, other than diabetes mellitus, to suggest chronic pancreatic insufficiency. Treatment of the diabetic ketosis presumably ameliorated only that increment of hyperlipemia to which ketosis contributed, without restoring lipid levels to normal. It is to be anticipated that the therapy instituted would not be capable of sustaining normality in lipid concentration of the blood. The apparent lability and rapid fluctuations in the patient's serum lipids suggest that, even in the absence of advanced vascular insufficiency, this patient may well represent an early example of the syndrome described by Adlersberg and Wang (20). The therapeutic approach toward this patient must be one of combined diabetic regulation and dietary measures aimed at maintaining low serum lipid levels. The latter might most readily be accomplished by the supplementary use of antilipemic agents.

SUMMARY

A case of idiopathic familial hyperlipemia in a 41 year-old white male diabetic is presented. Failure to adequately control the patient's diabetes resulted in the development of ketosis, accompanied by serum lactescence with enormous elevation in the serum triglycerides, eruptive xanthomata, lipemia retinalis, and hepatosplenomegaly. All the clinical manifestations of this condition responded satisfactorily to the restoration of diabetic control and maintenance of a restricted fat intake, with the exception that all fractions of the serum lipids failed

to return to normal, but only to a level where frank lactescence disappeared. The clinical findings and course of events serve to differentiate the underlying metabolic abnormality from diabetes mellitus with secondary hyperlipemia.

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DIAGNOSTIC CONIZATION OF THE UTERINE CERVIX IN PREGNANCY

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The diagnosis of carcinoma *in situ* of the cervix during pregnancy has usually been suspected on the basis of abnormal cytologic smears, to be confirmed ordinarily by multiple punch biopsies. Because of the frequent difficulty in differentiating physiologic pregnancy changes of the cervical epithelium from neoplastic changes, many pathologists have been reluctant to make a definite diagnosis of carcinoma *in situ* at this time. Cold knife conization of the uterine cervix in pregnancy has only rarely been utilized as a diagnostic aid. This report has two objectives: First, to emphasize that the microscopic diagnosis of pre-invasive carcinoma of the uterine cervix can and should be made during pregnancy and the methods of obtaining tissue for study should be the same as in the non-pregnant state. Second, to illustrate in a case report a technique by which cold knife conization of the cervix during pregnancy may be rendered feasible and safe for mother and fetus.

The uterine cervix undergoes alteration during pregnancy (1). It becomes edematous and very vascular. One may find a decidual reaction in the stroma and there is often eversion of the cylindrical endocervical epithelium with secondary inflammatory changes. The endocervical canal becomes the site of reserve cell proliferation and squamous metaplasia. The stratified squamous epithelium of the ectocervix becomes thicker, and responds to the endocervical eversion by epidermidizing these areas. Basal cell hyperplasia, the most important and controversial histologic change, is found in 10 to 20 per cent of pregnant cervixes (1-3). This lesion may arise in the endocervix as a product of reserve cell hyperplasia, and occurs somewhat less frequently in the basal layers of the ectocervix and in areas of epidermidization. The true site of origin is often impossible to determine. A majority of these hyperplastic epithelial alterations will revert to normal within six months after delivery (1-4). Lesions that have not disappeared by this time tend to persist and even progress. The degree of hyperplasia in pregnancy can be marked, and there may be some cellular atypism and incomplete loss of epithelial stratification. Some of these anaplastic changes will produce suspicious cytologic smears (5). The cases of basal cell hyperplasia with more atypism are less likely to revert to normal (3, 6).

Many cases of basal cell hyperplasia are not limited or even related to pregnancy, but represent coincidental findings (4, 6, 7). Their incidence and rate of reversion are the same, irrespective of pregnancy. Persistent cases of atypical hyperplasia are of great importance, for they may be coexistent with preinvasive carcinoma or eventually progress thereto (5, 8). The finding of basal cell hyper-

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plasia with degrees of atypism should not be regarded lightly at any time. The patient exhibiting this lesion deserves diagnostic conization of the cervix and careful follow-up. Hellman suggested that epithelial dysplasias arising in the endocervix are usually reversible and directly related to the pregnancy, although identical changes may be produced in this area by unopposed estrogen stimulation, infection, and trauma (1). He considers the atypical hyperplastic changes in the ectocervix in a different category, independent of pregnancy or hormonal stimulation and less often reversible. There is no agreement as to whether the endocervical or ectocervical lesion is more significantly related to subsequent carcinoma, although invasive carcinoma in general probably originates more often in the cervical canal than on the ectocervix.

The epithelial changes in the cervix during pregnancy have on occasion obscured the histologic criteria for the diagnosis of carcinoma *in situ*. There has been a tendency on the part of many observers to procrastinate with a suspicious lesion into the puerperium, and to make a definite diagnosis of carcinoma *in situ* only in persistent lesions. Greene and Peckham (9), Marsh and Fitzgerald (10), and Carter (11) have objected to this indecisive approach. These authors feel strongly that a definite diagnosis can and should be made during pregnancy. Greene and Peckham do not require complete loss of stratification as one of the diagnostic criteria, but do insist on nuclear abnormalities in all layers (9).

Cervical cytology, as well as histology, reflects the cellular changes occurring in the ecto- and endocervix during pregnancy, and there has been similar hesitation in making an absolute interpretation of Papanicolaou smears taken at this time. With increasing experience, longer follow-up studies, and a growing understanding of the histologic changes of pregnancy, greater certainty has been achieved in the evaluation of cytologic smears taken during gestation. Nieburgs and Clyman state that during pregnancy "only the parabasal cell dyskaryosis, if associated with marked hyperchromasia, is considered an adequate cytologic basis for a suggestive interpretation of carcinoma *in situ*" (12). Today cervical cytology is considered an important and reliable screening technique and guide in the detection of atypical and malignant cervical lesions during pregnancy (5, 13-15).

The entity of carcinoma *in situ* of the cervix is the same, irrespective of pregnancy. It has the same incidence, approximately 0.5 per cent, in both pregnant and non-pregnant women and does not seem to be influenced in any way by one or more pregnancies (5, 11, 13). Evidence is accumulating that true carcinoma *in situ* is an irreversible lesion (2, 9-11, 13). A resume of the reported cases of carcinoma *in situ* diagnosed during pregnancy and followed for at least six months postpartum shows that approximately 80 per cent of the lesions persisted. The "disappearance" of one fifth of these lesions has been explained on the basis of either complete removal at the time of original biopsy or incorrect interpretation of the pathologic changes at that time. Greene and Peckham pointed out that the same rate of "disappearance" existed in those cases of preinvasive carcinoma diagnosed and followed in the non-pregnant state, and probably for the same reasons (9).

The diagnostic problem in the non-pregnant patient is to rule out invasive carcinoma of the cervix. Carcinoma *in situ* is often found in the surface epithelium immediately adjacent to areas of invasive carcinoma (5, 8). Cold knife conization of the cervix may find evidence of this invasion not revealed by multiple punch biopsies. This diagnostic error in one large series was 3.6 per cent (9), and in another analysis 7.5 per cent (15). There is every reason to assume that at least the same percentage of error will obtain during pregnancy. Yet cervical conization to rule out invasion has rarely been performed in the parturient. An incomplete diagnosis, based on a reluctance to perform cold knife conization of the cervix in pregnancy, carries an overwhelming risk for the patient. Whereas the five year survival rate of patients with invasive squamous cell carcinoma of the cervix treated prior to the 34th week of gestation does not differ appreciably from that of the non-pregnant state when compared stage for stage, this rate drops to less than 25 per cent when the diagnosis is made or treatment deferred to term or the puerperium (16, 17). It is obvious that a secure diagnosis of carcinoma *in situ* during pregnancy is imperative, and therefore cervical conization must not be deferred to the postpartum period if it can be carried out safely.

CASE REPORT

A. R. (MSH # 142287), a 43 year old Puerto Rican gravida 3, para 2-0-0-2, was first seen in the Prenatal Clinic of The Mount Sinai Hospital in January, 1960. The expected date of confinement was June 23, 1960. Her last delivery had been in 1938. Menstrual periods had been regular, with no intermenstrual or post-coital spotting. The history and physical examination were within normal limits; the cervix was unremarkable on inspection. Routine cervical cytologic smears were taken, and reported as showing large numbers of cells with changes suggestive of atypical hyperplasia. Repeat smears one month later again showed marked atypical hyperplasia. Accordingly, the patient was admitted to the hospital in the 26th week of gestation for further diagnostic procedures.

In the operating room, under general anesthesia, the patient was placed in the lithotomy position and the cervix visualized and painted with Lugol's solution. Five punch biopsies were taken around the circumference of the squamocolumnar junction. Bleeding from the biopsy sites was brisk, and figure-of-eight chromic catgut sutures were necessary to secure hemostasis at each site. The estimated blood loss was approximately 400 cc, and the patient required one unit of blood to restore the blood pressure which had dropped. The post-operative course was benign. Pathologic examination showed scattered areas of excessive squamous cell epithelial proliferation; in one area there was marked cell atypism and many mitoses throughout all layers. No infiltration could be found. The interpretation was that of carcinoma *in situ*.

Further cytologic studies of the cervix continued to show grossly abnormal cellular morphology. In the 32nd week of gestation, when the baby was considered to be fully viable, the patient was readmitted to the hospital for conization of the cervix.

In the operating room, under general anesthesia, the cervix was exposed and grasped in four quadrants with Allis clamps. Inspection revealed that the portio vaginalis of the cervix was three centimeters long, the external os two centimeters dilated, and the internal os closed. A #5 braided surgical silk suture was passed submucosally as a purse-string at the junction of the rugose vagina with the smooth portio vaginalis of the cervix. The bladder was not advanced, nor was any attempt made to reach the level of the internal os. The suture was not fixed to the cervical substance, and was tied with only moderate tension to avoid cutting through the edematous tissues. A cold knife conization of the squamocolumnar junction and the distal three fourths of the endocervix was then accomplished with

ease; the apex of the cone reached the level of the purse string suture. Bleeding, in contrast to the previous procedure, was negligible. Four Sturmdorf-like sutures of #0 chromic catgut were placed in the four quadrants of the cervix, both to control slight oozing from the mucosal edges and to reconstruct the cervix. Neither vaginal packing nor vasoconstricting solutions were utilized. The patient's postoperative course was uneventful; there was no vaginal bleeding, onset of uterine contractions, or pyrexia. The microscopic pathology of the conization specimen again revealed preinvasive carcinoma.

Subsequent cytologic studies of the cervix consistently demonstrated only "slight epithelial dysplasia". In the 38th week of gestation, the patient entered the hospital in early labor. Under spinal anesthesia, a female infant in good condition weighing 3940 Gm was delivered by classical cesarean section. As part of the same procedure, a total abdominal hysterectomy including a cuff of vagina and a right salpingo-oophorectomy were performed. The patient had an uneventful postoperative course.

The microscopic pathology of the surgical specimen revealed residual preinvasive carcinoma high in the cervical canal. In addition, one focal area in this region showed superficial infiltration of malignant cells. Because of the now altered microscopic diagnosis, the patient received external radiation to the pelvis.

DISCUSSION

Conization of the uterine cervix in pregnancy has four practical hazards and one theoretical objection. The hazards are: hemorrhage, onset of labor, secondary cervical incompetence resulting in pregnancy wastage, and rupture of the amniotic sac during the procedure. The theoretical objection concerns the removal of the entire diseased portion of the cervix by conization, which prevents follow-up with respect to possible regression. This latter objection becomes less valid the more experience indicates that definitive diagnoses of carcinoma *in situ* can be made during pregnancy on histologic criteria and without demonstrating persistence of the lesion postpartum.

There have been isolated reports of cold knife conization performed during pregnancy. Greene and Peckham (9) reported conization in five pregnant patients, but did not specify technique or discuss complications of the procedure. Schmitz and his co-workers (5, 18) have carried out cervical conization over a period of years in cases where preinvasive carcinoma has been diagnosed by multiple punch biopsies. These authors insist that a diagnosis of carcinoma *in situ* cannot be established safely without adequate cone material. The total number of pregnant cases coned is not reported, nor was technique discussed; with respect to complications, they stated only that conizations were not responsible for any interruption of pregnancy (5). There was no obvious reluctance to perform this procedure, one conization being executed as late as the 35th week of gestation, and five cases of invasive cervical carcinoma were discovered in this way. Carter simply mentioned that in his experience with cervical conization in pregnancy abortion and premature labor were not encountered (11). Ferguson and Cavanagh (14) and Offen and Ferguson (19), reporting on the same series of cases, have performed conizations during pregnancy from the 8th to the 38th week. Their technique involves injection into the cervix of large volumes of vasoconstricting solution, use of a suction cautery, lateral cervical sutures for both hemostasis and traction, and postoperative packing of the defect. However, the hemostatic effects of the combined technique in pregnancy as compared to

the nonpregnant state "are not quite as dramatic, and a larger blood loss may be anticipated." At the time of the initial report, seven of the ten vaginal deliveries following this procedure had been premature. Beecham and Andros carried out cervical conization during pregnancy with the aid of a submucosal purse string suture similar to the one suggested in this report (20). The suture material employed was absorbable #1 chromic catgut, so that the suture was intended solely for purposes of hemostasis. These authors found two cases of invasive carcinoma in over two dozen patients coned, but the procedure was often performed on the basis of positive cytologic changes and without prior punch biopsies. Vaginal delivery was permitted in all cases except those with invasive carcinoma; one patient coned in the 36th week of gestation delivered uneventfully 48 hours later. Scott and co-workers described a technique for cervical conization whereby an "intracervical tourniquet" is produced by the injection of a saline-adrenalin solution into the cervical stroma, followed by coagulation of the defect (21). Conization by this method has been performed in all trimesters of pregnancy "without a single pregnancy loss." Finally, Stander and Lein indicated that they have utilized cervical conization during pregnancy and cite their prerequisites for the procedure (22).

Much experience has accumulated in our department in the use of the submucosal purse string (or Shirodkar) suture for correction of incompetence of the internal os of the cervix during pregnancy (23, 24). The procedure is simple and quickly executed. It was noted on repeated occasions that bleeding, encountered in varying amounts in the initial steps of the Shirodkar procedure, was immediately controlled once the purse string suture was placed and tied. It seemed that this type of suture might obviate or minimize all of the practical hazards encountered in cold knife conization of the pregnant cervix. By compressing the deep blood supply, relatively good hemostasis might be provided in the distal portion of the cervix. Application of the suture has never induced premature labor in our hands; to the contrary, increasing the cervical resistance in this manner was effective in some cases in minimizing the effects of an irritable uterus. The Shirodkar suture, specifically intended to treat cervical incompetence, would prevent secondary incompetence and pregnancy wastage. Finally, the constricting effect of the suture, placed just below the internal os of the cervix, would provide a protective barrier to accidental nicking of the amniotic sac during the procedure. From this reasoning, it appears that a Shirodkar purse string suture passed around the cervix prior to conization should make the procedure simple and safe for both mother and fetus.

Several details are of importance. The suture material employed must be of a permanent, non-absorbable nature in order to derive not only the short term advantages of hemostasis and protection of the amniotic sac, but the long term benefits of protection against cervical os incompetence and premature labor. The precise manner of passing this suture has been extensively described elsewhere; we feel that superficial placement of the suture is important to provide a safety factor against severe cervical lacerations or rupture of the lower uterine segment if labor should supervene before the suture can be removed (23). Vaginal

and cervical packing should be avoided, since they might stimulate uterine contractions; additional hemostasis, if necessary, should be achieved with catgut sutures used in the conventional manner.

The level at which the purse string suture is placed about the cervix will depend on how high the cone is intended to reach. In non-pregnant patients, the internal os is not reached in many conization procedures; the residual area of endocervix is often curetted at the same sitting (15). In the gravid patient, the level reached by cervical conization has not been specified in the reports cited above. We feel that extending the cone to the internal os or curetting the proximal portion of endocervix in a pregnant uterus imposes a great risk on the incumbent pregnancy, namely inadvertent amniotomy. Therefore, passing the Shirodkar suture at the level where the rugose vagina meets the smooth portio vaginalis, without mobilization of the bladder, permits excision of the distal three-fourths of the endocervical canal.

Conization in the non-gravid state is subject to some error and incompleteness (15). During pregnancy, the procedure may be even less reliable. To obviate the situation developed in the case report, it is suggested that all patients shown by cervical conization during pregnancy to have carcinoma *in situ* be delivered by cesarean section near term but prior to the onset of labor. Definitive treatment should await the results of a more complete diagnostic conization after the puerperium.

SUMMARY

A. The microscopic diagnosis of carcinoma *in situ* of the uterine cervix can and should be made during pregnancy.

B. Failure to diagnose and treat invasive carcinoma of the cervix before the 34th week of pregnancy materially worsens the patient's prognosis.

C. The only relatively certain means of ruling out invasive carcinoma is microscopic study of tissue obtained by cold knife conization of the cervix; this must be performed irrespective of pregnancy or the stage thereof.

D. The indication for diagnostic conization of the uterine cervix during pregnancy is the finding of basal cell hyperplasia with cellular atypism or pre-invasive carcinoma on punch biopsy. Conization should not be carried out without prior cervical biopsy.

E. A technique to minimize the dangers inherent in cervical conization during pregnancy is described.

F. The diagnostic limitations of the conization procedure during pregnancy are discussed.

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A PSYCHOLOGICAL ANALYSIS OF APPARENT DEPRESSION FOLLOWING RAUWOLFIA THERAPY*

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INTRODUCTION

In the past three years there have been many reports of depressive reactions in patients following the administration of the Rauwolfia preparations (1-6). Such reactions have constituted a major contra-indication to a full utilization of these compounds in the treatment of many illnesses. In this study, an attempt was made to establish objective criteria for the predication of depression in those patients prone to respond in this manner to the Rauwolfia drugs.

MATERIALS AND METHODS OF INVESTIGATION

Fifty consecutive patients from the Hypertension Clinic and Dermatology Clinic were the subjects of this investigation. These patients were studied by means of psychological tests, autonomic reactivity, and psychiatric interviews before, during and after the administration of the Rauwolfia compounds. The psychological tests included the Rorschach, Thematic Apperception, Bellevue-Wechsler, and Figure Drawings. The epinephrine-mecholyl test (Funkenstein Test), a sensitive indicator of autonomic reactivity, was utilized in an attempt to determine whether patients receiving Rauwolfia fall into predictable categories of depressive potential (7-10). The psychiatric interviews emphasized the present mental status, the past history, the psychodynamics, and the current adaptational maneuvers of the patient. Special attention was given to any disturbance of motor activity, mood, ideational content, and socialization.

The subjects consisted of 26 males and 24 females who were predominantly in the 40 to 55 year age group. Forty per cent of the group were of socio-economically deprived Puerto Rican and Negro origin, who were however within the average range of intelligence. The patients comprising the other sixty per cent of the group fell into similar categories of socio-economic and intellectual status. Nearly every patient was or had been married. Patients in the hypertensive group were chiefly in the early phase of their physical illness (six months duration), while the patients in the dermatological group were chiefly in the chronic phase of their physical illness (three to five years duration).

Two drugs were used. Raudixin® was administered to 47 patients with a daily oral dosage of from 50 to 400 mgm. Three patients received from 1 to 5 mgm of Serpasil® by mouth every day.

All patients were followed for twelve to eighteen months while the drug was

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being taken. Multiple base-line studies were performed on each patient. In addition to the initial psychological test batteries, psychiatric interviews and autonomic tests, all patients received a complete medical work-up including electrocardiogram, chest x-ray, and liver function tests. They were then seen once weekly by the psychiatrist and were subjected to two or more autonomic tests as well as one or more psychological tests during this study.

The psychologists and psychiatrist independently, on the basis of their findings, placed the patients into three groups. There were only three cases in which the psychologists and psychiatrist differed as to the depressive potential of the patient, and this was only a question of degree; *i.e.* high potential versus moderate potential. The three groups were as follows:

Group I: Those patients with a high potential for developing a depression: 11 patients.

Group II: Those patients with a moderate potential for developing a depression: 15 patients.

Group III: Those patients with a low potential for developing a depression: 24 patients.

The predictive criteria used were the following:

(a) Indications in the past history of any previous depression. (b) Indications of disturbance in mood, psychomotor activity, or intellectual functioning. (c) Indications of a chronic sense of guilt associated with unfulfilled aspirations, ambitions, or obligations. (d) Indications of the presence of an intensely ambivalent attitude toward some love object, coupled with a powerful emotional dependence upon this love object. (e) Indications of a sense of total rejection and abandonment at the hands of the social environment. (f) Indications of a sense of frustration or despair in the face of shrinking personal horizons and diminishing physical capacities. (g) Those patients who responded with a Group VI or VII reaction to the Funkenstein Test were weighted toward the hypothesized depression-vulnerable group. Our feeling was that since most patients who have a depression and respond well to electroshock fall into this group; these patients might be already autonomically primed for a depression, without its clinical manifestations.

RESULTS

The psychological test findings and the clinical interviews revealed the following predominant emotional pattern in the hypertensive group (26 patients). There was a minimum of overt phobic, hysterical, or obsessional neurosis. The patients were characterized by obsessive character traits and were reserved, conventional, and perfectionistic. Thirty per cent disclosed psychotic trends or their potential.

These patients manifested an overt facade of adequacy and self-reliance, but conscious feelings of inferiority and inadequacy were also present. There was an absolute minimum of acting out and aggressive outbursts in this group, with the exception of one patient.

Generally, these patients were overtly adequate as parents, but they derived minimal pleasure from their parenthood. Heterosexual activity was also adequate, but again there was a minimal pleasure. Although these patients had moderate intellectual, vocational, and social strivings, there were frequent failures in the attainment of these aspirations.

The general psychodynamic pattern of this group of hypertensive patients was their marked need for status, security, affection, and dependence. Unconscious rage, generated by the frustration of these needs, tended to be continuous rather than periodic. These patients had a great deal of difficulty in handling and expressing their anger, a problem existent since early childhood. The expression of anger seemed to carry with it a great risk—loss of maternal love and its derivatives, namely, affection, security, approbation, and prestige. In order to retain this affection and approbation, they have developed the technique of placation so as to preclude any possibility of jeopardizing their standing in the eyes of people upon whom they are dependent. A typical comment made by a patient when asked to describe himself was "I am easy to get along with. It has to be real hard for someone to get me angry." When asked what might get him angry, he replied, "If someone hits me." Another striking defensive maneuver was *activity*. Many of these patients had several jobs and found it difficult to relax. "I'm always happiest when I'm doing something anything," was another typical comment. It should be noted that this was basically a pattern of psychomotor activity and not reactivity to their environment.

The 24 patients in the group with skin disorders were characterized by general overt timidity and passivity. In contrast to the hypertensive group they showed more anxiety, more overt hysterical and obsessive features with greater inhibition in assertive and aggressive areas. They had much closer familial and environmental ties and demonstrated minimal adequacy in marital, parental, and vocational areas. Although these patients also had infantile dependency needs, anxiety was the predominant affect rather than rage. They were particularly prone to panic in relation to participation in adult sexual, marital, and parental activities. Guilty-fear and expiatory activity was also a predominant dynamic pattern in this group. Psychomotor activity as a defensive maneuver was rarely utilized by this group of patients.

Another feature of our series of patients was that eight subjects had previous histories of depression requiring psychiatric help, and two of these patients received electroshock treatment. None of these patients were excluded from this study, although they were classified at the time of observation as having subclinical, if not overt depressions.

The hypertensive and dermatological groups fell into all of the six groups of autonomic responsivity as enumerated by the Funkenstein Test. There was no predominant grouping except for a slight propensity for Groups VI and VII on the initial testing. This is the grouping in which most depressed patients respond autonomically.

Group I	8 patients
Groups II and III	13 patients
Group IV	7 patients
Group V	4 patients
Group VI	14 patients
Group VII	4 patients

Although our patients were predominantly between the ages of 40 and 60, the time of life when statistically most depressions occur, *not one case of true depression* occurred in our series; (using as criteria of the depressive syndrome the three basic components of (a) dejected, apathetic mood, (b) slowing down in thinking, and (c) the inhibition of instinct and will). None of our patients became excessively self-deprecatory, suicidal, troubled by morbid thoughts or feelings of being "blue", "low", or weeping. There were few complaints of anorexia, weight loss, insomnia, constipation, or early morning awakening.

Twelve patients responded with a "pseudo-depression", a reaction of excessive tranquilization, with diminished *psychomotor activity* as the chief symptom. They complained principally of being "slowed down," "tired," and "lacking push," while on the drug. Eleven of these twelve patients were from the hypertensive group. The drug seemed to cause a retardation of the excessive psychomotor activity, which in these patients had become an important and habitual pattern of adaptation. Repeat psychological tests and clinical interviews gave no indication of a true depression in this group. When the dosage level of the drug was readjusted so that the patients were not "over-tranquillized," their complaints disappeared. In no case was it necessary to eliminate the administration of Rauwolfia to these patients. Again, it seems worthwhile to note that in the dermatological group of patients, where excessive psychomotor activity was not a predominant pattern, there was only one case of over-tranquilization; (a patient who was given an exceedingly high dose of Serpasil[®], 5 mgm O.D.).

In reviewing the psychological test batteries after the study was completed, the following points emerged:

(a) There were 14 patients from the hypertensive group in whom excess psychomotor activity was mentioned as an important defensive reaction. Every one of the 11 patients who responded with a "pseudo-depression" was in this group.

(b) There was one patient from the dermatological group with this defense, but he did not respond with an "over-tranquilization" reaction.

(c) In regard to the Funkenstein Test, 16 of our patients shifted into Group VI and VII, the group where depressives usually fall. Since the Rauwolfia compounds are adrenolytic agents, this shift was not unexpected (11-12). It would appear that something else is necessary, in addition to the shift of autonomic reactivity, to create a depression. (The relationship of autonomic reactivity and depression has been explained earlier in greater detail (13-15).)

(d) Our preliminary predictions of patients prone to respond to these drugs with a depression, or "pseudo-depression," showed very little correlation with

our findings. Only 3 of the 12 patients responding with a "pseudo-depression" were put in the "high potential" group prior to being given the drug.

SUMMARY

It is of course very easy to theorize from little data; in our case only fifty patients were followed for twelve to eighteen months. Depressive reactions, reported in the literature, might have occurred in a larger series of patients, or if they had been observed longer. Within these limitations however, our data suggest the following theoretical formulations:

(A) The Rauwolfia compounds do not appear to be a causal agent in bringing about the "depressive" reactions which have been encountered in their use. It is felt that the untoward reactions have nothing to do with the physiological effects of the drug *per se*, but rather with the way in which the physiological effects psychologically threaten the patient. The patient who appears to be most prone to develop a "pseudo-depressive" reaction to these compounds is the individual who feels threatened by being calmed, made less active, becoming tired or weak, who tends to use psychomotor activity as a means of reassuring himself that he is adequate, and who fears passivity. Under the influence of the enforced relative passivity physiologically produced by these drugs, the patient may react with anxiety or a "pseudo-depression". In essence, this chemical interference with the patient's defenses, imperfect though it may be, without substitution of something more useful to the patient, tends to disrupt the patient's previous adjustments.

(B) In our series there were five cases of overt depression treated with Rauwolfia compounds. In three cases, their agitation was controlled; in the other two cases, the symptomatology was not exacerbated. Again, this is further evidence to support the thesis that these drugs are not truly depressogenic.

(C) The Funkenstein Test does not appear to be of value in correlating shifts of autonomic reactivity with changes in clinical symptomatology in these instances.

(D) Our findings raise the question of the relationship of Rauwolfia drugs and depressions; *causal or coincidental*. It is our hope that this paper will stimulate further careful investigation into this problem.

ACKNOWLEDGEMENT

We wish to thank Milton Mendlowitz, M.D. (Department of Medicine), Irwin Kantor, M.D. (Department of Dermatology), and Fred Brown, Ph.D., Leon Laski, M.A., Charles Graydon, Ph.D. (Department of Psychiatry) for their collaboration.

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Clinico-Pathological Conference

DIABETES AND COUGH WITH NEURITIS AND GANGRENE

Edited by

FENTON SCHAFFNER, M.D.

A 72 year old white retired peddler was admitted to The Mount Sinai Hospital because of weakness and pains in his extremities for several months. Ten years earlier he had been said to have diabetes mellitus and x-rays then showed densities in both lung fields, more on the left. He had a cough productive of mucoid and mucopurulent sputum and numerous episodes of hemoptysis over a period of several years. In addition he had wheezing and dyspnea on exertion for many years. Two years later he developed mild arthritis in his extremities and back, for which he received small doses of steroids intermittently. Several months before admission he developed weakness of both lower extremities and both hands with muscle wasting, 20-pound weight loss, some swelling of his hand and foot joints and numbness. The numbness was likened to standing on cotton. The patient also dropped things because he could not feel them. He became so weak he was confined to bed.

Six days before admission to this hospital, he entered another hospital because he was unable to raise either foot and he fell when he tried to stand. Sphincteric function was intact. The patient was very depressed and cried easily. He had been depressed in the past and had attempted suicide twice several years earlier. The skin of his legs had been treated with x-ray therapy about two years prior to admission because of ulcerations on the sides of his legs. The physical findings and laboratory test results were the same as obtained later in this hospital. He was transferred here for further evaluation.

On examination his temperature was 100.2° with a normal pulse and blood pressure. He was poorly nourished and his tongue was smooth and reddened. The AP diameter of his chest was increased and fine crackling rales were heard in the left lower lung field. Expiratory wheezes were heard bilaterally. Heart sounds were normal. The liver was felt two fingerbreadths below the right costal margin and was slightly tender. A firm spleen tip was felt. Testicular atrophy, poor rectal sphincter tone and smooth enlargement of the prostate were noted. Deforming arthritis of the hands was present with pain on motion of the shoulders and elbow. Motion of the neck was also limited. The small muscles of both hands and lower extremities were wasted and a bilateral foot drop was present. Hypesthesia and diminished proprioception, thermal and vibratory sensation were noted in all four extremities. No fasciculations or abnormal reflexes were found. The left calf had some hemorrhagic scaling skin lesions with sharp and elevated borders.

Chest x-ray showed interstitial infiltrations in both lungs, which were emphysematous. The left costophrenic angle was blunted due to thickened

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pleura. Rounded lucencies were seen in each lung and were thought to be bullae. The heart was not enlarged and the aorta was tortuous. Review of serial films indicated that little change had occurred in ten years. Electrocardiographic changes were nonspecific and included atrial premature contractions, ST depressions and diphasic or low T waves in 2, 3 and aVF, T waves were also diphasic or low across the entire precordium.

Throughout the hospital stay the hemoglobin ranged between 11.2 Gm per cent to 10.1 Gm per cent and the white count between 7,000 per cu mm to 9,000 per cu mm except for one count of 18,000 per cu mm two weeks before death. Differential counts were all normal and averaged about 65 per cent segmented leukocytes, 20 per cent band forms, 12 per cent lymphocytes and the rest monocytes or eosinophiles. Sedimentation rate was 86 mm/hr, twice. Many blood cultures, LE preparations and a Coombs test were negative. The urine contained a trace to 1+ albumin with from 1 to 15 white cells and occasional red cells. Urine culture grew *A. aerogenes* and enterococci. Glycosuria was never found. Stool examinations for blood, ova and parasites were negative. Prothrombin times, BUN, serum calcium, phosphorus, bilirubin, acid and alkaline phosphatases and cephalin flocculation were normal. Fasting blood sugars were normal but on a glucose tolerance test the blood sugars rose to 190 mg per cent, 200 mg per cent, 209 mg per cent and 179 mg per cent at $\frac{1}{2}$, 1, 2 and 3 hours respectively with no glycosuria. The serum albumin was 2.5 Gm per cent and globulin 3.4 Gm per cent twice and protein electrophoresis also showed low albumin with high alpha 2 globulin. Congo red excretion was 66 per cent of the injected dye. No free acid was present in the fasting stomach but 120 units was present 45 min. after histamine. Thyroidal I^{131} uptake was 34 per cent. Spinal fluid was clear. Pressures, dynamics, cell counts, proteins and cultures were all normal. Blood and spinal fluid serology were negative. Sputum cultures showed *Candida albicans*, coagulase positive hemolytic staphylococcus aureus, beta hemolytic streptococci and *A. aerogenes*. No acid-fast organisms were seen. Liver biopsy specimen was normal. Skin and muscle biopsies showed only muscular atrophy and nonspecific inflammatory and regressive changes in the skin. Bone marrow was hypercellular with some granulocytic hyperplasia.

In the hospital the patient continued to complain of weakness and joint pains. He continued to run a low-grade fever with occasional higher spikes despite various antibiotics. Furthermore, the findings in the chest remained unchanged by auscultation and x-ray. After two months in the hospital, gangrene of the toes of the left foot developed. He was given steroids without apparent effect. The gangrene extended and involved both legs. A large area of necrosis developed on the right leg with no inflammatory reaction. At the end of the third month in the hospital, he became more emaciated, hypotensive and was found dead early one morning.

*Dr. Richard A. Bader**: I was reminded when I read this case history and tried to decide what the patient had, of the quatrain from Omar Khayyam:

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*Myself when young did eagerly frequent
Doctor and Saint, and heard great Argument
About it and about: but evermore
Came out by the same door as in I went.*

Basically, by history, we have a man presumed to have diabetes mellitus, some chronic pulmonary disease characterized by bilateral pulmonary infiltrations, wheezing, hemoptysis and dyspnea. A two-year story of arthritis, some lesions of his leg and some neuropathy or neuromuscular disorder suggest that are dealing here with some diffuse systemic process; whether it is related to the lesion or an independent process remains to be seen.

On physical examination this man was suffering with bronchiolar or bronchial obstruction, emphysematous changes in his chest, and probably peripheral neuropathy. I say probably because of the loss of all modalities of sensation in both motor and sensory components. The fact that there were no abnormal reflex changes would tend to eliminate some long tract disease of the cord. Chest x-ray showed interstitial infiltrations of the lungs which Dr. Wolf will describe.

Dr. Bernard S. Wolf†: A film of the chest was striking. We had actually three examinations of the man during a three week period. The most outstanding features were the densities in both hilar regions, more marked on the left (Fig. 1). Most of these densities were in the hilae as confirmed by oblique and lateral projections. In addition, streaks extended into the periphery of the lung fields. These were not normal pulmonary markings but linear strands of varying thickness. Between the strands lucent areas were seen sometimes ovally shaped in the upper left lobe, and sometimes quite angular in shape. They had the appearance of bullae. Both lungs were emphysematous in a rather generalized fashion. Both domes of the diaphragm were unusually low in position. The transverse diameter of the heart appeared to be somewhat increased and the left ventricular contour of the left margin of the heart was somewhat globular in configuration. The aorta was tortuous. The trachea was displaced somewhat to the right. From a roentgen point of view, this was the so-called bullous emphysema, which in almost all cases is associated with interstitial fibrosis and inflammatory changes. It was not the picture of bronchiectasis. It is seen in late silicosis and occasionally as an end stage in Boeck's sarcoid or late in Christian's disease. In most of the cases that look like this one did, no specific etiology is found and it is labeled as bullous emphysema associated with chronic interstitial inflammatory fibrosis of unknown etiology.

Dr. Bader: We have a chest film which shows bullous emphysema, some increase in fibrous tissue markings of the lung root which could have been an old burned out inflammatory process, as burned out Boeck's sarcoid or burned out silicosis. There is some axis deviation present on the electrocardiogram which suggests the type of pattern one might see due to chronic pulmonary

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hypertension. This type of electrocardiogram indicates possible nonspecific myocardial involvement plus changes secondary to chronic lung disease affecting the pulmonary artery pressure.

The man's chief complaint when he entered the hospital was peripheral neuropathy. I think a good starting point would be to begin there and work from that point of view. The peripheral neuropathy was bilateral and involved all extremities. This suggests a diffuse process. It most likely was toxic or metabolic since it was so symmetrical; for which there are many diseases such as periarthritis nodosa and amyloidosis which can cause isolated neuropathies, I am not talking about pressure neuropathies. It is very unusual for diseases which cause vascular involvement of a specific nerve root to cause such bilaterally uniform neuropathy.

Since this man was diabetic, the first thought that comes to mind was that this was diabetic neuropathy. Diabetic neuropathy can be of several types. The most common type, well recognized by most clinicians, is the diabetic neuropathy involving the lower extremities usually associated with marked pain and sensory involvement and rarely with motor involvement. The picture in our case certainly



FIG. 1. Chest x-ray showing hilar densities.

does not represent the common variety of diabetic neuropathy. Diabetic neuropathy can cause marked motor involvement. When diabetic neuropathy involves all four extremities with marked sensory involvement, it presents a Guillain-Barré type of syndrome. This is called diabetic neuronitis and is characterized very commonly by an elevated spinal fluid protein. Here spinal fluid protein was not elevated and therefore it is less likely that this was diabetic neuronitis. Diabetes mellitus can cause a chronic low-grade peripheral neuropathy with a stocking type of hypesthesia. In favor of diabetic neuropathy we have symmetry, the fact that he was diabetic and the fact that patients with minimal glycosuria may have very severe atherosclerotic and neuropathic disturbances. Further in favor of diabetic neuropathy is the presence of peripheral gangrene in the hospital. In spite of the fact that we were not told what type of pulses the patient had, it certainly suggests that he had diabetic gangrene. Against diabetic neuropathy is the fact that there was motor and sensory involvement without much pain and without elevated spinal fluid protein. The latter also speaks against Guillain-Barré type of syndrome.

It was not likely to be amyotrophic lateral sclerosis because he was old for the disease, his muscle wasting was not associated with fibrillation or fasciculation and hyperflexia with lower motor neuron degeneration was absent. Periarthritis nodosa is known to cause peripheral neuropathy from time to time. However, there are several features about this case which do not fit periarthritis. For example, his blood pressure was normal. His renal findings were minimal. He had no eosinophilia of true allergic background, muscle or abdominal pain, and the symmetrical involvement of all four limbs by neuropathy would be a little unusual in periarthritis nodosa. In favor of periarthritis nodosa are the facts that he has generalized joint pains, hepatosplenomegaly, cutaneous lesions that were necrotic, peripheral gangrene which can occur and usually does terminally, and elevated globulins. However, he did have pulmonary findings. Pulmonary findings in periarthritis are those of eosinophilia pneumonia or episodes of asthma with infiltrations in both lungs such as Löffler's pneumonia. I would be surprised if the lung lesions did show eosinophilic pneumonia. It looks more like bullous emphysema. On x-ray we must consider other diagnoses.

There are diffuse conditions such as amyloidosis that can cause peripheral neuropathy, but this is exceedingly rare. In favor of amyloidosis would be the neuropathy and skin lesions while against it would be the normal Congo red excretion, lack of significant cardiac failure or cardiac symptoms, lack of marked renal findings and albuminuria and the fact that liver biopsy was normal. Finally, several other diagnoses are less likely but should be mentioned for the sake of completeness. While he did not have any adenopathy, he had the lesions on the leg which were irradiated. They could have been the result of some lymphoma and he could have had some lymphomatous process at the base of the lungs because he had a bullous emphysema with some infiltrative or fibrotic process. I do not think it is likely. Another possibility is metastatic bronchogenic carcinoma with peripheral neuropathy. Although he had hemoptysis for ten years, there was no change in the chest x-rays according to the protocol. Von Wegener's

syndrome usually has cartilaginous lesions in the upper respiratory tract and has more marked renal abnormalities. In the absence of cartilaginous lesions and severe renal involvement, I would doubt that the process was Von Wegener's syndrome.

I think it is very unlikely that this was histiocytosis, considering the man's age and the fact that the clinical picture is not explained. This syndrome usually produces a diffuse mottled appearance in the chest x-ray causing an alveolo-capillary block and not obstructive emphysema.

This man had skin lesions described as reddish-brown. Kaposi's sarcoma can cause this type of involvement. Indeed, in the case reported from this hospital, there was invasion of the hilar areas by inflammatory neoplastic tissue. In favor of Kaposi's sarcoma would be the fact that it occurs in males more commonly from 60 to 70 years of age and he did receive radiotherapy which is given for this condition and there are reddish brown plaques which are described and it can cause lung lesions. However, against this is the fact that Kaposi's sarcoma is never necrotic and these lesions were described as necrotic two years earlier. Kaposi's sarcoma is accompanied by edema and the patient did not have edema. Finally, Kaposi's sarcoma rarely causes gangrene.

I think I am left with two basic considerations. If we search for a single diagnosis, we would have to think of periarteritis to explain his neuropathy and arthritis, chronic asthmatic condition from previous years, associated with bullous emphysema, and diabetes mellitus.

If we are thinking of a multiple diagnosis, we have to take diabetic neuropathy with peripheral vascular disease, gangrene, peripheral neuropathy, bullous emphysema, and rheumatoid arthritis. As far as the skin lesions are concerned, we would have to attribute them to diabetic necrosis.

Of the two, while I would like to lean toward periarteritis because it would explain his hyperglobulinemia and joint pain, the involvement of all four extremities forces me away. It is so unusual that I think I have to think of a more diffuse toxic metabolic process such as diabetic neuropathy or one of the unusual neuropathies seen in toxic metabolic disorders such as poisonings or some cryptic malignancy.

*Dr. Mortimer Bader**: I should make the other diagnosis, so one of us will be correct. I will say periarteritis nodosa.

Dr. Alexander B. Guitman†: I think I would agree with one of the Drs. Bader. I do not know quite which one. The story does strongly suggest diabetic neuropathy to me because of the symmetry and the general course of events. The thing that is not explained so far is the very marked weight loss because everything that has been described would hardly account for this course. I think we must be prepared to have some lesion in addition to those already presented and I have been wondering what that would be. I suppose it can be narrowed down to either a generalized infection, of which tuberculosis should be considered very seriously, or a neoplasm tucked away somewhere in the chest that was not

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recognized in the x-ray. Dr. Popper would be terribly disappointed if nothing was said about the liver in this case because I cannot conceive of a case being selected for clinical pathological conference without some hepatic abnormality. In any diabetic, although much has been written about the hepatic changes, the fact is that very little is found. I am sure if we will look carefully, we will find something more than fatty degeneration. The liver was enlarged and it was also tender, which is not common. I wonder whether it was not the site of some infectious involvement—particularly tuberculosis or a neoplasm.

*Dr. Hans Popper**: We turn now to the pathological findings. Before we show the autopsy findings, we have a challenge from Dr. Gutman. The liver biopsy specimen as the report read failed to reveal any significant changes. Perfectly normal liver structure was seen.

Dr. Bader asked the question as to the biopsy findings of the skin. In the skin a somewhat thickened vessel showed slight intima proliferation but nothing which would have caused the one reporting the specimen to consider periarteritis nodosa.

We now turn to the autopsy findings. The cause of death in this instance probably was pericarditis, associated with bilateral empyema, more on the left side. The purulent material contained a variety of bacteria in the pericardial and both pleural cavities such as *B. coli* and streptococci. The heart itself weighed 420 Gm. It was enlarged and, as Dr. Bader told us it would be, particularly the right heart. There was considerable dilatation of the right atrium and right ventricle with flattening of the myocardium and widening of the bicuspid valve. In the right atrial appendage a thrombus was found lodged in the somewhat dilated atrium. We recognized some dilatation on the left side but less than on the right with no valvular changes. A considerable amount of myofibrosis obviously related to coronary sclerosis was present. We also found rather recent myomalacia which again was a reflection of the coronary sclerosis which this patient had. There was a somewhat disturbing feature in that myocarditis was noted in areas of perfectly well preserved myocardial fibers, and therefore it was not a result of myofibrosis or myomalacia. We looked for eosinophilic cells and we could not demonstrate them. It was an interstitial myocarditis of a nonspecific nature. This could have a variety of causes. One of them could be mineral imbalance with changes in serum potassium. Others could be anoxic changes or some kind of hyperallergic reaction.

With this finding as background, we turned now to the inspection of the liver. I have already said that the biopsy specimen failed to reveal any significant changes. There were some changes found in the autopsy specimen. The liver was not significantly enlarged. It weighed 1400 Gm. The increased size on clinical examination was probably a reflection of a low diaphragm, in view of the emphysema, as well as the empyema. The normal architecture was distinctly exaggerated as in passive congestion. On microscopic examination, central necrosis was seen. These hepatic changes probably were the result of heart

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failure which we would have expected from the appearance of the heart itself. There was nothing specific in the liver except for the presence of so-called glycogen nuclei in the peripheral zone of the lobule. These nuclei have no distinct diagnostic qualifications except that they appear far more frequently in diabetes and with the increased blood sugar curve we would like to associate them with the presence of diabetes.

The prostate was distinctly enlarged, pointing to benign hypertrophic changes which failed to produce any obstruction.

The kidneys presented somewhat of a disappointment. They had a fairly smooth surface and were somewhat enlarged as found in persons of this age group. On microscopic examination there was a slight degree of arterial sclerosis with nonspecific thickening of the smaller arteries of the kidneys without involvement of the arterioles or the glomeruli in keeping with the normal blood pressure (Fig. 2). Needless to say, no evidence of diabetic sclerosis was present.

We have presented a nonspecific group of changes so far: slight right-sided cardiac hypertrophy, arteriosclerotic heart disease with passive congestion, and the cause of death, terminal pericarditis. We have to search for the underlying changes. The testes were atrophic but in addition the arteries were distinctly thickened and their lumens were narrowed. There was obstruction of the lumen in some areas complicated by the presence of a few inflammatory cells. This was a diffuse chronic fibrotic disease of arteries which was entirely nonspecific in the testes. We turned to the gastrointestinal tract and were impressed by a very conspicuous dilatation of the esophagus with thickening of the muscle in the esophagus near the cardia. We assumed that probably a mild degree of

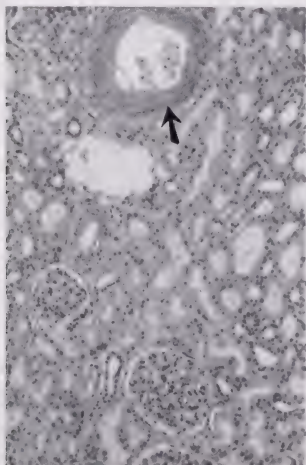


FIG. 2. Section of kidney showing slight sclerosis of a renal arteriole (arrow) (H & E).

cardiospasm must have existed in the patient and microscopically the effect on the esophagus was seen to probably be the result of spastic changes which may not have been significant in the entire picture of the patient. As we looked at the outer layers of the esophagus, we again were impressed by arterial changes. The arterial changes were more specific in the testes in that in the esophagus the intima was very thickened. The muscle layer apparently was not always involved. The nerves were fairly normal in appearance. We found not only intimal thickening which possibly could have been associated with arteriosclerotic changes but also we found something which is never seen in simple arteriosclerosis, namely, disruption of the elastic layer. This fragmentation of the elastica was the remnant of an arterial disease. This was an old healed or scarred arterial disease in which sometimes necrosis or other severe alteration of the muscular layer of the arteries had now been replaced by a scar. Since the elastica never regenerates, the defect of the elastica is permanent.

Since we were alerted to the presence of fibrotic arterial disease, we looked at the stomach and found in the submucosa scarring arterial lesions. Nothing of this nature was found in the liver, the kidneys or the heart muscle. In the cecum a fairly extensive area of necrosis of the mucosa was seen. The mucosa was interrupted and the submucosa was exposed and scarred. This was the result of active arteritis. However, this acute arteritis could have been on the basis of an ulcer and we have to be cautious in assuming this to be the cause or the result of the ulcer. In this instance, the acute and inflammatory changes with thrombosis probably were the result of the ulcer. In other areas on the base of this ulcer, we saw chronic obstruction with alteration of the media and beginning recanalization. This was chronic arteritis and periarteritis in the intestinal tract. We raised the question of periarteritis, peculiar as it was, because of its distribution and because of the tremendous scarring, indicating a long duration of the arteritic changes. We found them in the classical areas, the testes, the gastrointestinal tract and in the gallbladder, but nowhere did we note acute periarteritis. The pancreas was of interest in view of diabetes. Microscopic examination of the pancreas failed to reveal any significant changes except for arterial involvement (Fig. 3). Whether diabetes was the result of a chronic arteritis of the pancreas is a challenging thought, which cannot be proven at this time.

In the adrenals, circumscribed areas of necrosis were noted. The adrenal is one of the sites of predilection of acute arteritis. Here was one of the few areas where acute fibrinoid necrosis still was present with obstruction of lumens occasionally and periarterial remnants of inflammatory exudate.

We now turned to the skin lesions. The extremities had large ulcerative areas with dry gangrene. An area of skin near the necrosis quite distinctly showed severe arterial changes. However, there was recanalization of the vessels and there was chronic arteritis with no eosinophilic changes. That was probably one of the most active areas of cell infiltration with active fibrosis. The vessels near the gangrene were clearly obstructed by old necrosis which had none of the earmarks of an arteriosclerotic process but more the signs of an arteritic process inflammatory in nature.

This brought us to the skeletal muscle system. In the skeletal muscle, we

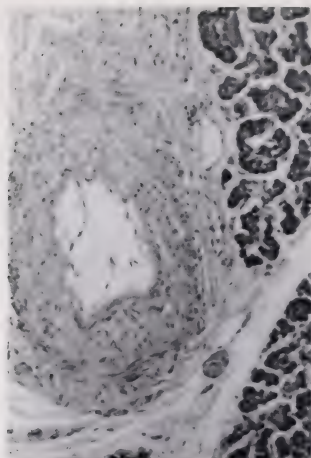


FIG. 3



FIG. 4

FIG. 3. Section of pancreas with chronic fibrosing arteritis in a larger artery (H & E).

FIG. 4. Acute arteritis with minimal inflammation in skeletal muscle with obstruction of lumen (arrow) (H & E).

saw arteritic changes of various ages such as obstructed vessels with only very little acute inflammatory changes (Fig. 4) and acute subsiding inflammatory changes with fragmentation of the elastic layer. There was also aneurysm formation, as expected after interruption of the elastic layer by periarteritis nodosa. Even more important for clinical correlation, sections through the peripheral nerves showed quite clearly arteritis accounting for the neurologic changes.

I have warned Dr. Bader before that we unfortunately would be unable to show any findings from the brain because brain examination was not permitted. However, sections of the lumbar spinal cord showed no significant demyelination. The most important finding was that the interior spinal artery showed an old periarteritic process.

There was no relation to any hyperallergic process. It was not angiitis. It involved the larger arteries and was chronic and healing. Actually, despite the large number of sections, we were completely at a loss to show anywhere the characteristic segmental arteritis which we consider typical of periarteritis nodosa. In lieu of a better explanation for the time being, we had to call this periarteritis nodosa with diffuse systemic involvement and could explain very nicely the clinical picture, except for the lung.

In the spleen which is supposed to be enlarged in periarteritis, we did not find any arterial changes in the splenic arteries. There was severe congestion

and severe reticuloendothelial hyperplasia associated with the presence of a large amount of vacuolated material. This was chronic splenitis with reticuloendothelial hyperplasia associated with severe fatty fibrocytosis. We did not find significant changes in the bone marrow which would be related to this peculiar fat storage in the spleen. The lymph nodes were not changed. However, the lymph nodes of the lung showed a very peculiar alteration. The architecture and principal features were preserved but large vacuoles had granulomatous tissue around them (Fig. 5). On further inspection quite clearly giant cells were seen developed around these vacuoles. We suspected before that we were dealing with some peculiar fat storage problem and sudanophilic material was present in the lymph nodes with reaction around it.

That brings us to the lung where we must connect the changes which have been presented so far with what on x-ray gave a rather peculiar picture. We have already learned that probably a pulmonary lesion with pericarditis was the cause of death. The terminal cause of death in a debilitated patient may not even be associated with the significant clinical manifestations. In the left lung we saw a large number of cavities and one in the right upper lobe (Fig. 6). They were not emphysematous cavities but were filled with an oily material and were surrounded by many little granulomas scattered throughout the lung with only a slight amount of pulmonary sclerosis. The cavities had a fairly smooth wall.

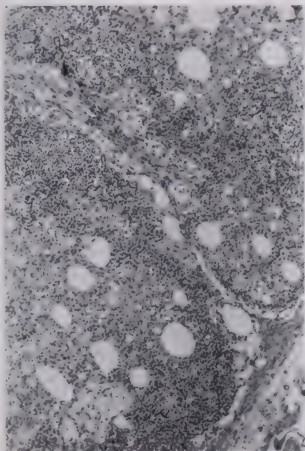


FIG. 5



FIG. 6

FIG. 5. Section of hilar lymph node with normal architecture but containing numerous vacuoles (H & E).

FIG. 6. Gross appearance of right lung with cavity in upper lobe (open arrow) and embolus in artery to lower lobe (solid arrow).

They were darkly pigmented and had ridges extending into them. Around them some granular inflammatory lesions were found and some small granulomatous foci. The smooth wall failed to be lined by any epithelium. There was a sclerosing pigmented granulomatous tissue with vacuolization. Old cavities were apparently scarred, fibrosed and healed. They were not the smooth healing cavity of tuberculosis. We failed to see any tuberculosis process. The cavities were bronchiectatic and were partially still connected with the bronchi which showed old inflammatory changes. Some nodules were seen which were areas of induration formed by fibrotic granulomatous lesions. The sclerosing granulomatous lesions apparently occasionally underwent central breakdown. On section an oily material oozed out raising the question of lipid pneumonia. Microscopic study showed us that apparently all these cavities were lined with fat, leading to the foreign body granulation tissue around them. We had a typical chronic lipid pneumonia of long standing with lipophages. There was anthracotic granulation tissue around this fat which was slowly being organized (Fig. 7). We have to assume that this lipid pneumonia led to the chronic fibrotic changes with alteration of the elastica. The elastica was disrupted near the fat and showed peculiar changes. This was also associated with new formation of fibers. Can we relate this in any way to the changes of the vessels? The lung showed in many areas subacute or chronic pneumonia and with many lipophages. The vessels were distinctly

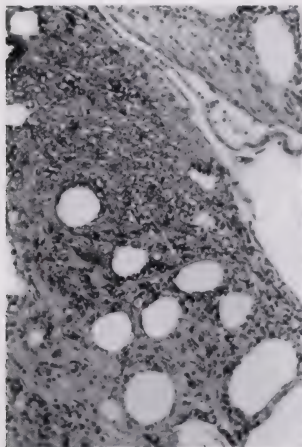


FIG. 7

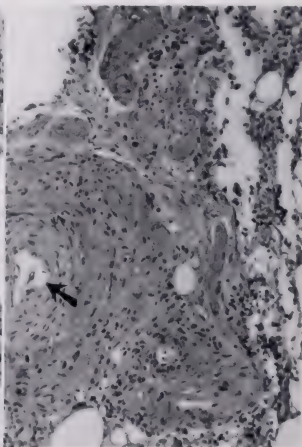


FIG. 8

FIG. 7. Vacuoles in pulmonary tissue surrounded by fibrosis and anthracotic cells (H & E).

FIG. 8. Chronic pulmonary arteritis with narrow lumen (arrow) (H & E).

enlarged. Upon microscopic examination we found the same changes which we already demonstrated in other vessels (Fig. 8). In typical periarteritis nodosa, the lung is usually not involved. We saw here elastica destruction and disturbances which resulted in the same changes of a chronic arteritis in the lungs which we had shown in the other organs. When we did fat stains, we found fat around the vessels in the smaller vessels; some fat also was in the arteries.

It remains for us to try to correlate the findings which we have presented. We felt that we were dealing with a chronic lipid pneumonia, most probably from mineral oil. Why should this patient who had this lesion for ten years have a lipid pneumonia? We know that lipid pneumonia results from either debilitation or it may result from medication with mineral oil in the form of sprays (1-4). However, this patient must have had cardiospasm and I wonder whether this may not have been responsible for the lipid pneumonia. The chronic lipid pneumonia produced x-ray findings, a productive cough, wheezing and emphysema. We saw lymph node reaction and splenic reticuloendothelial hyperplasia, suspecting this material found its way to these sites (2). In addition a chronic, recurrent periarteritis was present. We suggest that the lipid material may have been the irritant producing the somewhat unusual arteritic changes (1, 2).

You may ask if it is known that lipid pneumonia produces generalized arteritic changes. We looked in the literature and found one fully established case in which there was involvement of the kidney, the spleen, the adrenals and the ovaries with acute severe periarteritis in the presence of lipid pneumonia (5). We indeed believe that the pulmonary arteritis without any question was the result of the lipid pneumonia (1-3). The periarteritis produced clinical symptoms with right sided cardiac hypertrophy and involved the esophagus, stomach, testes, gallbladder, adrenals and cecum. The pancreatic condition produced diabetes which was reflected in the glycogen nuclei in the liver cells. The diabetes may have aggravated the arterial changes but did not produce periarteritis nodosa. The muscle involvement could be related to the myositis; the peripheral nerves and spinal cord involvement would give the neurological changes. The terminal events were infection of the lipid pneumonia, empyema, pericarditis and cardiac manifestations.

In conclusion then, we can say that two diseases were surely present: lipid pneumonia which as such contributed only to the terminal infection, plus a peculiar type of periarteritis. We submit the hypothesis that the two are related.

Final Diagnosis: LIPID PNEUMONIA. ARTERITIS OF LUNGS, PANCREAS, GASTRO-INTESTINAL TRACT, SKIN AND MUSCLES (POSSIBLY SECONDARY TO LIPID PNEUMONIA). DIABETES MELLITUS. GENERALIZED ARTERIOSCLEROSIS. BILATERAL PURULENT EMPYEMA AND PURULENT PERICARDITIS (TERMINAL).

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Radiological Notes

BERNARD S. WOLF, M.D.

CASE NO. 114

This was the first admission of a 44 year old female. Thirteen years prior to admission, the patient had an episode of severe pruritus followed by erythema and then darkening and toughening of the skin. Shortly thereafter, she noted the onset of Raynaud's phenomena which have persisted although somewhat abated until the present time. She then began to complain of dysphagia which has been progressive. Four years prior to this admission, the diagnosis of cardiospasm was made. The patient had most difficulty in swallowing veal or beef and apparently had little trouble with fowl or fish. She also complained of occasional regurgitation. Physical examination was negative except for pigmentation of the skin of the arms, legs, chest and abdomen, and thickening of the skin of the face, neck, breast, arms and legs. The tips of both index fingers were flattened as a result of necrosis or infection presumably associated with the Raynaud's phenomena. "Hemoglobin was 13.4 per cent Gm. White blood count was not remarkable. Gastric analysis showed free acidity to 50 units and a total acidity of 70 units. Barium swallow (Fig. 1) showed a ring or web with a maximum diameter no more than 7.5 mm located about 5 cm above the hiatus of the diaphragm. There was no delay to the passage of fluid barium through the esophagus and into the stomach. The esophagus was not dilated proximal to the ring. However, an opaque pill 12.5 mm in diameter did not pass the site of the ring despite prolonged observation. The elongated, rather wide, sac-like viscus distal to the ring showed thick folds resembling gastric rugae. There was no evidence of any gross ulceration or inflammatory change. The roentgen diagnosis was made of a "lower esophageal ring" of non-distensible type located at the esophagogastric epithelial junction (1, 2).

Thoracotomy was performed and the esophagus was exposed down to the level of the hiatus. At first sight, there appeared to be no evidence of a hiatus hernia or of a stricture in the esophagus. Careful palpation, however, revealed a circumferential thickening about 5 cm above the diaphragm. A longitudinal incision into the lumen was made through the thickened area. It was then evident that there was a rather substantial web or diaphragm protruding into the lumen. The mucosa proximal to the web was squamous epithelium while gastric rugae began immediately distal to the web. Careful exposure of the viscus distal to the web disclosed that there was a peritoneal sac which did not extend as high as the level of the web but stopped about an inch distal to the web. A plastic procedure on the esophagus at the site of the web was done. The longitudinal incision was sutured in a transverse fashion with a double layer of sutures. An attempt to perform a standard type of Allison hiatal hernia repair was not entirely successful because the phrenico-esophageal fascia appeared to insert at a

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point below the mucosal junction of the stomach and esophagus. Sutures were therefore passed between the esophageal suture line through the esophageal hiatus into the diaphragmatic portion of the phrenicoesophageal ligaments. By tying these sutures, the esophagogastric junction and hiatus were apposed.

Biopsy of the ring demonstrated that the junction of the squamous epithelium of the esophagus and the cylindrical epithelium of the stomach occurred at the level of the ring. The muscularis mucosa particularly on the esophageal aspect of

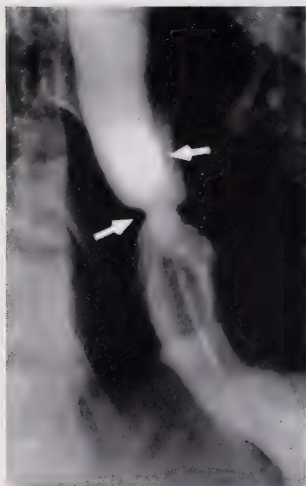


FIG. 1



FIG. 2

Case 114, Fig. 1. Barium swallow shows no delay to the passage of barium through the esophagus and into the stomach. About 5 cm above the hiatus, there is a web, diaphragm or ring (lower arrow) which fails to distend normally. Thick folds suggesting rugae are seen beyond the ring. A circular compressed barium pill (upper arrow) 12.5 mm in diameter failed to pass the ring. The size of this pill corresponds to a #36 Fr esophagoscope. The diameter of the lumen at the site of the ring is easily calculated by measuring the widths of the ring and of the pill on the film and setting up a simple proportion using the known diameter of the pill. In this case, the residual lumen at the level of the ring was 7.5 mm.

Case 114. Fig. 2. Film taken several months after plastic procedure shows persistent narrowing (upper arrow) which now appears more elongated. An opaque pill (lower arrow) of the same size as that used preoperatively passed this area promptly and is in the stomach. The film suggests that a small hernia may remain but it is not possible to decide this since the level of the hiatus could not be determined.

the ring was thickened. There was no evidence of inflammatory or scleroderma-tous change. Post-operatively, the patient has done quite well subjectively. Repeat barium meal examination (Fig. 2) about six months after the operation showed persistent narrowing at the site of the previously demonstrated ring. The narrowing at this time, however, was not web-like; an opaque pill one-half inch in diameter traversed this area promptly and without any difficulty. A skin and muscle biopsy taken at the time of thoracotomy from the skin of the chest wall failed to show any abnormality.

Final Diagnosis: NON-DISTENSIBLE ESOPHAGOGASTRIC RING.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. John H. Garlock

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CASE NO. 115

This was the first admission to this hospital of a 12 year old boy with the chief complaints of anemia and epigastric pain of five years duration. The pain occurred mostly at night, awakened him from sleep and was relieved by milk. Five years before admission, three and a half years before admission, and one and a half years before admission, the child had been hospitalized elsewhere for massive hematemesis and melena. The diagnosis on each occasion was that of a duodenal ulcer. It was subsequently determined that the child often vomited food shortly after eating and that he had lost 15 pounds in the preceding 18 months. Examination on admission showed a thin, poorly developed, pale boy appearing chronically ill. Hemoglobin was 6.1 Gm per cent. Previous barium meal examinations had presumably shown the second part of the duodenum to be deformed. Another barium meal was done before subjecting the patient to subtotal gastrectomy. This showed no evidence of duodenal deformity or ulceration. However, in the esophagus there was a constant stricture 3 to 4 cm in length beginning a short distance distal to the thoracic inlet (Fig. 1). The esophagus proximal to this was unusually distensible. The stricture measured about 3 mm at its narrowest point. The proximal portion of the narrowed area showed a somewhat funnel-shaped communication with the dilated esophagus above. The esophagus distal to the stricture was difficult to distend completely but appeared to have a tubular configuration. When the patient was prone and pressure was applied to the abdomen, distal to the tubular segment was a typical sliding hernia about 4 cm long with widening of the hiatus (Fig. 2). There was no marked delay to the passage of a fluid barium mixture through the esophagus into the stomach. In moderate Trendelenburg posi-

tion, barium flowed freely from the stomach below the diaphragm up into the hernial sac and esophagus.

Because of the unexpected finding of a stricture of the esophagus, further inquiry into the history was made. At about the age of four years, the patient had been rushed to a hospital because of sudden dysphagia. This was a transient

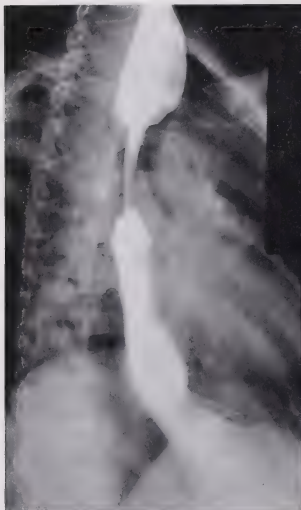


FIG. 1

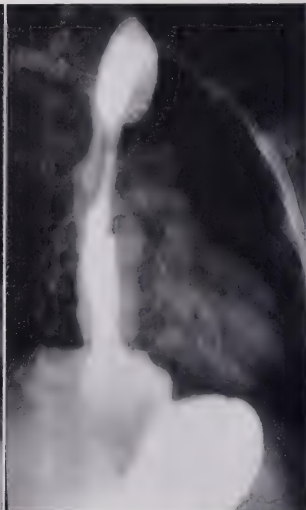
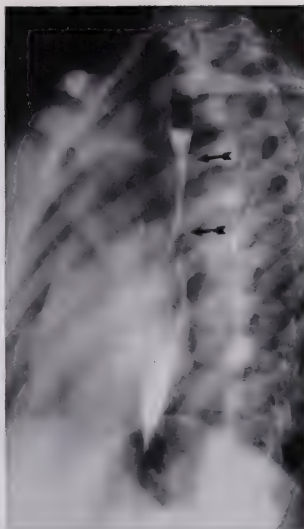


FIG. 2

Case 115, Fig. 1. Barium swallow shows a stricture 3 to 4 cm in length beginning a short distance below the thoracic inlet. The esophagus proximal to the stricture is markedly dilated. The structure or viscus distal to the stricture is tubular with slight irregularity of its contours. Thick folds are seen traversing a wide hiatus.

Case 115, Fig. 2. Barium swallow with patient prone and pressure applied to abdomen shows findings similar to Fig. 1. However, this maneuver demonstrates that a moderate sized hiatal hernia of globular configuration is also present. In other words, the "passageway" above the diaphragm shows four segments: (a) A short dilated portion proximal to; (b) an elongated stricture which is above; (c) a tubular segment which enters; (d) a sliding hiatal hernia. The tubular segment distal to the stricture is the abnormally lined distal esophagus. The strictured region is the result of a peptic esophagitis which extends into the squamous-lined proximal esophagus. The original nature of the epithelium lining the most severely strictured area cannot be determined since it is completely denuded epithelium.

Case 115, Fig. 3. Erect film taken four years prior to Figs. 1 and 2 shows the strictured segment (between arrows) to be essentially the same. This was not recognized at that time. The viscus distal to the stricture has the usual tubular configuration of esophagus. A sliding hernia is not demonstrated, presumably because the position of the patient was not favorable.



episode for which no cause was found. It appeared in retrospect that this child did not thrive in his early years as well as the other children in the family although this story was rather indefinite. Films of the esophagus taken about four years prior to admission were subsequently submitted and showed findings essentially similar to those found in the current examination (Fig. 3).

The impression from the roentgen examinations of the esophagus was that this boy was suffering from severe esophagitis associated with an abnormally lined esophagus, that is, the so-called Barrett anomaly in which a considerable portion of the distal esophagus is lined not by squamous epithelium but by cylindrical mucus-producing epithelium. This condition has been referred to as "gastric-lined esophagus," "the terotopic gastric epithelium in the esophagus" or "congenitally short squamous esophagus." Esophagoscopy revealed a marked reflux of acid gastric juice into the most proximal portion of the esophagus. At 22 cm from the incisor teeth, ulceration was seen to extend into a markedly stenotic segment which could be entered only after careful dilatation. There appeared to be a segment at least 2 cm in length with diffuse ulceration of the mucosa. Beyond the stenosis, reddish uninflamed mucosa was seen. Biopsies were taken from the proximal margin of the stenosis, from within the stenotic segment, and also beyond the site of stenosis. The biopsy from beyond the stenosis showed fragments of uninflamed gastric mucosa without chief or parietal

cells and the glandular epithelium seemed to be exclusively mucus producing. Biopsy from the stenotic segment showed ulceration suggestive of the bed of a peptic ulcer. Biopsy immediately proximal to the stenotic segment showed esophageal mucosa with severe chronic inflammation. It was clear that a peptic inflammatory change extended into squamous epithelium proximal to the stenotic segment but, since no epithelium was seen within the area of maximum stenosis, it could not be determined whether the ulceration at this site had occurred in squamous epithelium or in cylindrical epithelium. The esophagus distal to the site of stenosis was lined by cylindrical epithelium typical of the Barrett anomaly.

The child's swallowing ability improved after esophagoscopy. He was given several transfusions and begun on a regime of esophageal dilatation.

The roentgen findings in this patient are typical of the Barrett anomaly with associated peptic esophagitis. Most patients with this condition do not develop symptoms until the age of 40 or more despite the fact that the basic defect is congenital. This has been attributed to the slow development of a sliding hernia with resultant reflux of acid gastric juice into the abnormally and normally lined esophagus. Both portions of the esophagus are susceptible to peptic digestion. Discrete penetrating peptic ulceration is likely to develop in the abnormally lined portion while diffuse more superficial inflammation occurs in the squamous-lined portion.

Final Diagnosis: CONGENITALLY SHORT SQUAMOUS ESOPHAGUS ("BARRETT ANOMALY") WITH PEPTIC ESOPHAGITIS.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Alexander Richman and Dr. Max L. Som.

CASE NO. 116

A thirteen year old white female child was admitted for the fifth time with the chief complaints of nausea, vomiting and abdominal pain. About three and a half years prior to this admission, the family of this child suffered financial reverses and was forced to move elsewhere. On the first day of school in this new city, the patient complained of diffuse abdominal cramps followed by nausea and vomiting. She continued to vomit repeatedly, was hospitalized, and treated with intravenous fluids. At that time, she suffered many recurrences of these episodes lasting 15 to 20 minutes, coming usually just before going to school or after returning from school. Occasionally, an episode would awaken her from sleep. There was no relationship between these attacks and meals. They occurred both before and after eating although occasionally food would precipitate an attack. The patient distinguished the cramps associated with these attacks from pain experienced frequently in the epigastric region which was relieved by eating. She missed many days in school because of these episodes. The patient was hospitalized several times, for intravenous therapy. Two barium meal examinations were said to have been negative. Medical and psychiatric consultations

were of no assistance. The patient lost 25 pounds within a period of about a year. After returning to this area, the frequency of the patient's attacks decreased.

The child was originally admitted for diagnostic investigation two and a half years prior to the current admission. Examination showed a thin, well developed, intelligent and friendly girl. There were no positive physical findings. Hemoglobin was 11.3 Gm per cent; red blood count 4 million per cu mm. The stool was 4+ guaiac on one occasion but negative on several subsequent examinations. Barium meal examination, serial observations of the small bowel, barium enema examination, oral cholecystography and intravenous pyelography were reported as being within normal limits. No positive laboratory findings were obtained. The patient was discharged with the diagnosis of anorexia nervosa. The subsequent admissions were required because of episodes of abdominal pain and vomiting. On one of these occasions, which began with eating a frankfurter, the frankfurter was found in the vomitus four days after ingestion. Repeat barium meal examinations during these admissions were now reported as showing an irritable duodenal bulb and, on one occasion, the presence of a crater in the duodenal bulb was suspected. The proximal half of the descending



Case 116, Fig. 1. Barium meal shows an arcuate sharply outlined indentation (arrow) along the distal portion of the greater curvature of the stomach. The bulb appears deformed with a question of an ovoid crater within it. The duodenal sweep was irritable.

duodenum was markedly spastic and there was delay in the flow of barium through the transverse portion of the duodenum. There was also evidence of extrinsic pressure upon the antrum of the stomach along its greater curvature (Fig. 1) and to a lesser degree upon the descending portion of the duodenum (Fig. 2). The findings were interpreted as those of a duodenal ulcer associated with an inflammatory mass and or pancreatitis. On ulcer therapy, the child did well for approximately a year.

On the current or fifth admission, the patient complained of right upper quadrant pain and nausea and vomiting for nine days. The pain on this occasion radiated to the back and to the right shoulder. Physical examination showed a firm, hard mass in the right upper quadrant at the level of the umbilicus which appeared to extend towards the right flank. The mass was tender to deep palpation and appeared to be only slightly movable. There was spasm of the rectus muscle over the mass. Intravenous pyelography showed displacement of the upper portion of the right ureter laterally and the suggestion of a mass located retroperitoneally (Fig. 3). This displacement was not present on the previous pyelogram.

Because of the suspicion of neoplasm, exploratory laparotomy was performed. A cystic mass was found along the lower portion of the greater curvature of the stomach which was adherent to the head of the pancreas. This cyst communi-



Case 116, Fig. 2. In the lateral projection, a curved indentation (arrow) is seen along the anterior aspect of the duodenum distal to the bulb. This region is not normally distensible.



Case 116, Fig. 3. Intravenous pyelography shows an arcuate lateral displacement (arrow) of the upper portion of the right ureter. A poorly demarcated hazy density is present medial to this site and lateral to the spine.

cated with a cavity located retroperitoneally underneath the liver. Both the cyst and the cavity contained similar brownish fluid. The cyst was lined by gastric mucosa; portions of the wall removed were reported as consisting of smooth muscle covered by gastric mucosa, compatible with the diagnosis of a gastric duplication cyst. Portions of the wall of the retroperitoneal cavity, however, showed vascularized fibrous cyst wall lined by granulation tissue with focal hemorrhage, necrosis and acute and chronic non-specific inflammation, *i.e.* an abscess cavity. The septum between the cyst and the lumen of the stomach was incised and a broad communication established. The patient did well post-operatively.

In retrospect, the assumption that the mass related to the greater curvature of the stomach and the first portion of the duodenum was secondary to a duodenal ulcer was incorrect. The clinical picture did not substantiate the presence of an inflammatory mass which is quite rare as a result of an ulcer. This child went on, however, to develop such a mass retroperitoneally as a result of perforation of the gastric duplication cyst. This is a frequent occurrence in such patients and is presumably due to peptic ulceration within the cyst.

Final Diagnosis: GASTRIC DUPLICATION CYST WITH RETROPERITONEAL PERFORATION.

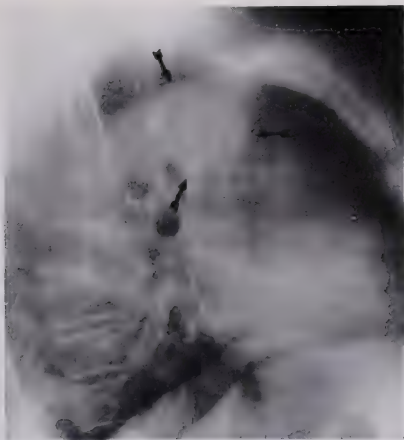
CASE NO. 117

This was the first admission of a 52 year old white male who was apparently in good health until six weeks prior to admission when he developed a cough and a "cold." After subsidence of the respiratory infection, the patient continued to be troubled with a constant dry hacking cough and persistent hoarseness with change in voice. Three weeks prior to admission, a film of the chest showed the presence of a "lesion." Bronchoscopy and direct laryngoscopy were performed. Bronchoscopy was negative but there was a paralysis of the left vocal cord.

Examination on admission showed a short rather obese male who was well nourished and not acutely ill. There were no significant physical findings. Blood pressure was 120/74. Hemoglobin was 18.8 Gm per cent; white blood count was 11,500 per cu mm. Electrocardiogram showed left axis deviation but no evidence of myocardial damage. On the admission physical examination, it was noted that there were several small subcutaneous, non-tender, rounded, freely movable masses about 1.5 by 1.5 cm in diameter in the left forearm, at the wrist and below the elbow. Sixteen years prior to admission, he had been told when examined for army induction that he was suffering from Von Recklinghausen's disease and was turned down on that basis.



Case 117, Fig. 1A. A lobulated homogeneous mass (arrows) is seen above the left hilum and adjacent to the mediastinal structures. The aortic knob, i.e. the posterior portion of the aortic arch, is seen through the mass indicating that these shadows lie in different frontal planes.



Case 117, Fig. 1B. In the lateral projection, the mass appears as an egg-shaped density (arrows) overlapping the anterior portion of the aortic arch and the trachea.

Roentgen examination of the chest showed a somewhat lobulated mass adjacent to the left superior mediastinum which extended as far backward as the posterior wall of the trachea (Figs. 1A & 1B). The roentgen and clinical impression was that of a bronchogenic carcinoma infiltrating the mediastinum. At exploration, however, a mass was found outside the lung, adjacent to the aorta in the region of the ductus. This was carefully dissected free and found to arise from the vagus nerve at the origin of the recurrent laryngeal nerve. The aorta was compressed, and at the site of origin of the subclavian artery appeared to be weakened. A plaque in the subclavian artery apparently ruptured during the course of resection. The opening in the aorta was sutured and multiple transfusions administered. Post-operatively, the patient did quite well. On microscopic examination, the tumor was a neurofibroma.

The diagnosis of carcinoma of the lung was too easily arrived at in this case and little attention was given to the presence of subcutaneous neurofibromata. However, a neurofibroma of the vagus nerve is extraordinarily uncommon and it is not likely that an unequivocal diagnosis of this condition can be made. The possibility, however, may be suggested and the surgeon prepared for a difficult dissection of a mediastinal tumor intimately related to the large vessels.

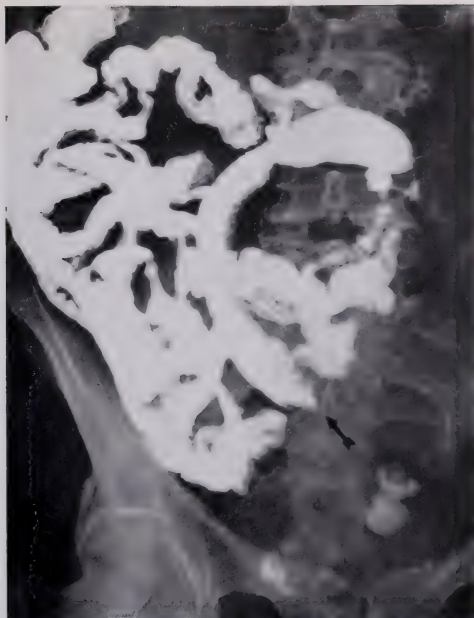
Final Diagnosis: NEUROFIBROMA OF THE LEFT VAGUS NERVE.

CASE NO. 118

This was the fourth admission of a 73 year old white female with the chief complaints of weakness of four weeks duration and tarry stools over a period of 14 months. The first admission about a year previously had been for the same complaint and this was also true of the subsequent admissions. Complete investigation had demonstrated no organic lesion of the gastro-intestinal tract. Investigation for a blood dyscrasia that might explain bleeding was also negative. The patient had been discharged from the hospital about two months previously and, in the interval, the hemoglobin, elevated by multiple transfusions to 13 Gm per cent had fallen to about 8 Gm per cent. Physical examination showed a chronically ill, anemic female. Except for a 1 cm nodule of the right thigh which



Case 118, Fig. 1A. Small bowel examination shows an elongated curved loop to the right of the lower spine which shows an abrupt termination near the brim of the pelvis. A peculiar, small, triangular collection of barium is seen at this point (upper arrow). There was slight delay to the passage of barium at this site. Irregular mottled amorphous calcifications are seen lower in the pelvis (lower arrows).



Case 118, Fig. 1B. At the termination of the loop shown in Fig. 1A (arrow), there is an acute angulation of the bowel followed by a short curved segment. This configuration was reproduced exactly on multiple examinations.

was considered to be a neurofibroma, physical examination was essentially negative. Pelvic examination was not satisfactory. Because of an atrophic vagina, the uterus could not be definitely identified. One observer felt that there was the sensation of a mass on the left side of the pelvis in the sigmoid region.

Small bowel examination done on four different occasions showed identical findings. There was a fixed, markedly angulated but unobstructed loop of small bowel on the right side above the level of the brim of the pelvis, not far from the mid-line (Figs. 1A & 1B). Adjacent to this loop, there was a large mass extending into the pelvis with irregular calcifications within it. It was believed that these calcifications were within large fibroids and that the small bowel was adherent to a fibroid uterus. It was also assumed that this fixation of the small bowel to the pelvis was not the cause of bleeding since no definite evidence of an intraluminal tumor defect or ulceration could be demonstrated.

Exploratory laparotomy was performed and a large tumor mass about 5 inches in diameter was found in the pelvis adherent to the dome of the bladder and also to a loop of small bowel. This tumor appeared to be encapsulated and was easily removed from the bladder but a portion of the small bowel had to be resected with the tumor mass. An independent ovarian cyst the size of an orange was noted on the right side of the pelvis. Examination of the specimen showed that the tumor was a large, nodular and somewhat lobulated hemorrhagic, partially cystic tumor arising from the outer aspect of the small bowel. At the site of attachment of the tumor, there was a dimplelike outpouching of the mucosa forming a small pseudodiverticulum in the depths of which a small ulcer was present. Histological examination showed a neurofibrosarcoma of low-grade malignancy. The patient has had no subsequent episodes of bleeding and has survived for more than five years.

Review of the films as described above show considerable similarity with the findings in Case #109 of these Radiological Notes. The calcifications noted in the pelvis which were assumed to be calcification within fibroids were located within the exoenteric neurofibrosarcoma.

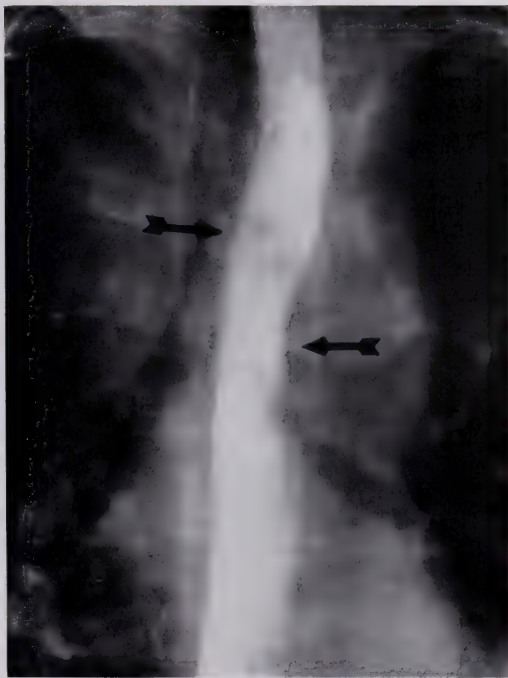
Final Diagnosis: EXOENTERIC NEUROFIBROSARCOMA OF THE SMALL BOWEL WITH CALCIFICATION SIMULATING UTERINE FIBROIDS.



Case 119, Fig. 1A. Barium swallow three weeks after start of radiotherapy shows lack of complete distensibility of the esophagus in the superior mediastinum with irregular serration or scalloping of the borders (arrows). Marked widening of the superior mediastinum is evident. Incidentally, a small hiatal hernia was also present (not shown).

CASE NO. 119

This was the first admission of a 64 year old female who for two years had been complaining of some loss of weight. More recently, however, difficulty in breathing and hoarseness appeared. Two months prior to observation, a mass had appeared on the left side of the neck and a chest film demonstrated a superior mediastinal mass. Aspiration biopsy of the supraclavicular mass was reported as lymphosarcoma. Radiotherapy with cobalt 60 was started to the neck and mediastinum but because of an exacerbation of dyspnea, the patient was admitted to the hospital for further therapy. Examination on admission showed an acutely ill patient with marked respiratory distress. Large nodes were palpable on both



Case 119, Fig. 1B. Re-examination three and a half weeks after the conclusion of radiotherapy shows essentially a normal appearance.

sides of the neck. In addition, there was evidence of a mass in the abdomen to the left of the umbilicus. A left recurrent nerve paralysis was present. The patient was anemic.

The course of this patient in the hospital was quite stormy. She was treated with nitrogen mustard and radiotherapy. Of interest for the purpose of this report was the development of difficulty in swallowing during the course of telecobalt therapy to the mediastinum. A 10 by 14 field over the anterior mediastinum and a similar field posteriorly were treated. Treatment was started carefully with doses of 50 roentgens per day but after a week this was increased to 200 roentgens per day to the anterior field and 200 roentgens per day to the posterior field. After about three weeks of treatment when exposure anteriorly had reached 2,600 roentgens and exposure posteriorly 3,000 roentgens, because of difficulty in swallowing, a barium meal was performed. This showed limited distensibility in the superior portion of the esophagus with irregular serration of the contours of the esophagus (Fig. 1A). These changes were consistent with a superficial inflammatory process, *i.e.* an irradiation esophagitis. Despite this, however, an additional 600 roentgens was given to the anterior field because the mass was responding quite poorly. This was given over a period of ten days. Three and a half weeks after the conclusion of treatment and a little more than a month after the original observations, re-examination of the esophagus was performed. The irregularity of contour previously seen had disappeared (Fig. 1B). The patient had no remarkable complaints of dysphagia at this time. About two weeks later, however, the patient required an emergency tracheotomy as a result of tracheal compression by the mediastinal tumor. The patient survived for an additional three and a half months but succumbed as a result of diffuse disease.

Radiation mucositis of the esophagus is not often demonstrated roentgenologically since the process in the large majority of instances is quite superficial. Moreover, it is only with special techniques or supervoltage therapy that substantial amounts of radiation are likely to be delivered to this region. In most instances, this is done for malignant neoplasm of the esophagus and radiation changes in the adjacent normal mucosa are ordinarily not sought or are obscured by the changes due to the neoplasm.

Final Diagnosis: RADIATION ESOPHAGITIS IN A PATIENT WITH LYMPHOSARCOMA OF THE MEDIASTINUM.

Surgical Techniques

4. VAGOTOMY AND PYLOROPLASTY FOR DUODENAL ULCER

JEROME W. CANTER, M.D., DAVID J. KAVEE, M.D., RAFAEL REISS, M.D.,
ISADORE KREEL, M.D., AND IVAN D. BARONOFSKY, M.D.

For the past year the operation of vagotomy and pyloroplasty has been used by the Department of Surgery as the definitive surgical therapy of duodenal ulcer. In conjunction with the Department of Gastroenterology, maximum secretory capacity of the stomach has been measured before and after operation

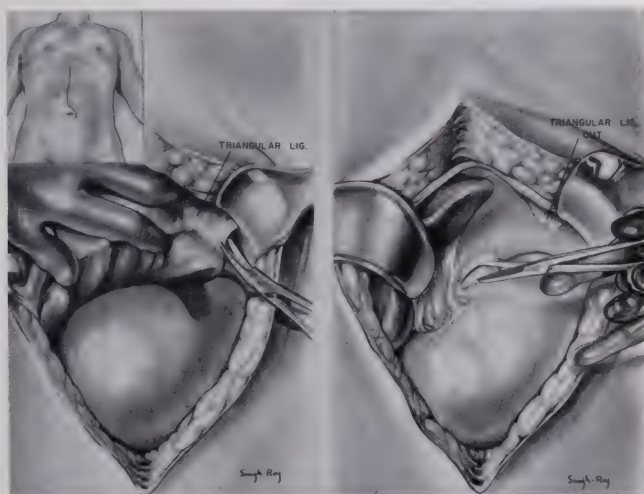


Fig. 1. The exposure at the esophageal hiatus is obtained by dividing the triangular ligament of the liver (left), and incising the peritoneal reflection over the esophago-gastric junction (right).

The section on Surgical Techniques is one of a series prepared by the Department of Surgery. Some of the techniques described are original, others are of long-established application, some with modification found useful here. The descriptions afford a concise review of techniques currently utilized at The Mount Sinai Hospital, New York.

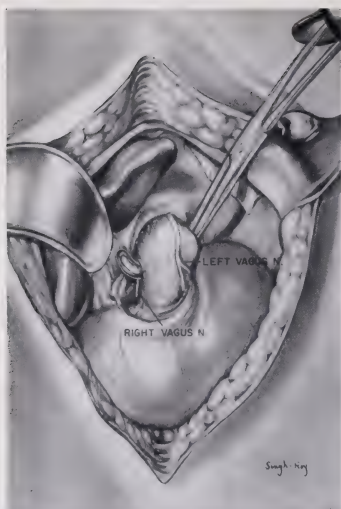


Fig. 2. The lower end of the esophagus is mobilized by blunt dissection. Note that the left vagus nerve is anterior, and the right vagus nerve is posterior and may lie in the periesophageal tissue.

Fig. 3. The main vagal trunks are ligated and divided under direct vision, as traction is maintained on the lower end of the esophagus.

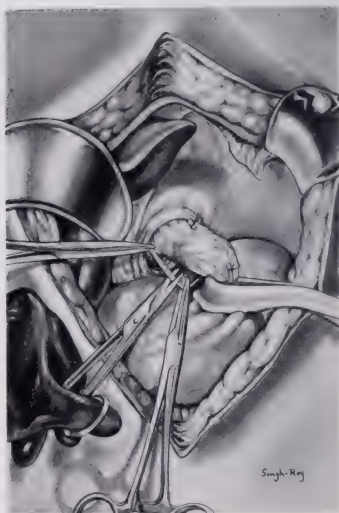


Fig. 4. The lower end of the esophagus is inspected and palpated for small nerve fibers. These are carefully divided.

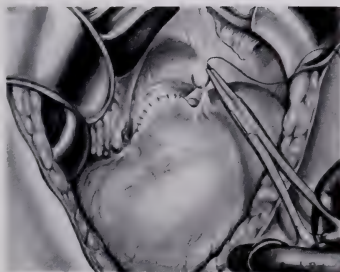
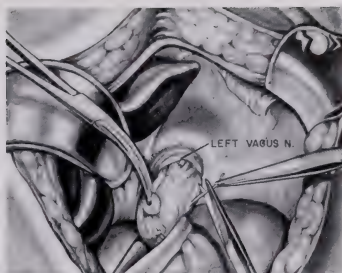


Fig. 5. The peritoneum at the hiatus is closed with interrupted fine silk sutures.

Fig. 6. The pylorus is incised midway between the lesser and greater curvatures. The anterior one-half of the pyloric sphincter is excised and the incision is continued for a distance of 3 cm on either side of the pylorus.



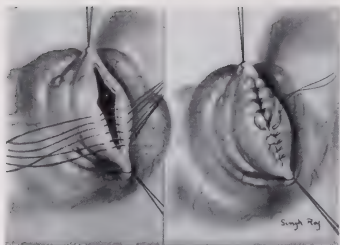


Fig. 7. The pyloroplasty is closed with interrupted fine silk sutures, in order to invert as little tissue as possible.

in these patients. This parameter has been used to estimate the effectiveness of the procedure, as well as the usual clinical follow-up.

Technique described herein incorporates what we consider to be the essential features of the operation. Emphasis is on the performance of a *complete* vagotomy under direct vision, with severance of all the small nerves at the esophagogastric junction, as well as the two main trunks. The pyloroplasty is of the Heineke-Mikulicz type, including an anterior pylorotomy (and excision of an anterior duodenal ulcer, if one is present).

Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital New York, N. Y.

The Filter Paper Virus Obstructing Test for Specific Antibody: Its Correlation with Standard Neutralization Test Methods. Walter L. Henley, M.D., Helen D. Zepp, Eugene Ainbender, M.D. Presented May 6, 1960.

We have found that if the lower edge of a strip of filter paper is dipped into a virus suspension, the virus rises up the paper in a regular, reproducible pattern. However, if serum containing specific antibodies against the virus is spread in a band across the paper, the rise of the virus is slowed or blocked.

Twenty-three sera were tested against each of the three types of the polio-virus by the filter paper method and simultaneously by two standard neutralization test methods. The neutralization test methods used were the constant serum method, the varying virus method and the constant virus serum dilution method. In 117 of the 126 tests there was agreement between the filter paper method and the serum dilution method—an agreement rate of 93 per cent. One hundred and thirty eight tests were done in which the filter paper method was compared with the virus dilution method. Agreement was found between the two methods in 129 of the 138 tests; a correlation rate of 93 per cent. In 126 tests the two standard neutralization tests were compared with each other. One hundred and sixteen of the 126 tests gave the same result; a correlation rate of 92 per cent. The differences observed are not statistically significant indicating that the filter paper method is as reliable as the two standard neutralization antibody methods now in use. This fact has important, practical implications.

The filter paper method requires only a drop of serum obtainable by finger puncture. It requires only one tissue culture tube, while the standard tests require a minimum of three tubes. Furthermore, the new method detects specific polio antibodies by the third day of illness, while the standard methods do not do so until the eighth to tenth day of disease. This may be due to the fact that the filter paper method is a more sensitive indicator of neutralizing antibody, or it may be that it measures a different antibody. The "obstructing" antibody may have a closer relationship to immunity than does the "neutralizing" antibody as measured by standard methods.

Use of Radioactive Poliovirus in Paper Strip Antibody Test. Ruth Berger, M.D., and Maria M. Hevitz. (From the Department of Pediatrics (Laboratory) of The Mount Sinai Hospital, New York.) Presented May 9, 1960.

We have shown that if the lower edge of a strip of filter paper is placed in a suspension of virus, the virus moves up the paper and becomes distributed upon it in a regular reproducible manner. The upward spread of the virus is diminished when human serum which contains specific antibody is placed in a band across the filter paper. By this method the presence or absence of poliovirus antibody

can be determined accurately with a single tissue culture tube and a drop of serum obtained by finger puncture. We have attempted to convert the method into a completely physical one, by the use of virus labelled with radioactive phosphorus. We have also used such virus to study the mechanisms involved in blockage of migration of virus by specific antibody.

The method we have used is as follows: Poliovirus is grown in tissue culture, in a medium which contains inorganic radioactive phosphorus. This phosphorus is taken up by the tissue culture cells; and when the virus multiplies in the cells, the P 32 is incorporated into the virus ribonucleic acid. The virus is then purified by centrifugation and ultra centrifugation; the final step in purification is accomplished by passage through a cellulose ion-exchange resin, diethylaminoethyl cellulose.

When we have used purified, radioactive poliovirus in the filter paper antibody test, we have found that human serum containing a high concentration of polioantibody markedly decreases the amount of radioactivity detected on the upper part of the paper strip. Virus also is absent in this part of the strip, this fact being shown by inoculation of half of the strip into tissue culture tubes.

When the serum contains no antibody against polio, the paper strip is almost uniformly radioactive, being high at the top as well as the bottom of the strip, and virus also is present throughout the length of the strip.

A Newly Discovered "Physical Marker" for Attenuated Poliovirus. Helen D. Zepp and Eugene Ainbender, M.D. (From the Laboratories of the Pediatric Department, The Mount Sinai Hospital, New York.) Presented May 9, 1960.

Mass vaccination of human beings with living attenuated poliovirus vaccines has been introduced in several parts of the world. The possibility of reversion in the human intestine of attenuated strain to neuro-virulence has aroused fears in the minds of many investigators. At the present time, attenuated poliovirus can be distinguished from virulent strains with certainty only by injection into the central nervous system of primate animals. This method entails intraspinal and intracerebral injection of monkeys and requires microscopic examination of many histologic experiments. It is wholly impractical for mass studies and cannot answer the question regarding possible reversion of attenuated strains fed to large populations. Therefore, biological "markers" have been sought with the hope that they might be of practical value in the laboratory which would detect attenuated from neuro-virulent strains. No satisfactory "markers" have been found so far. The two biologic "markers" in current use depend upon differences in growth between neurotropic virus and attenuated virus (T marker and at varying pH ranges D marker). Both of these "markers" are not reliable except for virus isolated from people who have been fed attenuated living polio vaccines.

We have sought a simple physical "marker" which would detect the difference between attenuated strains and neurovirulent strains of poliovirus and we believe that we have discovered such a "marker."

Purified neuro-virulent poliovirus strains are eluted from diethylaminoethyl cellulose ion-exchange resin columns with 0.02 M phosphate buffer in a repro-

ducible manner. Practically all the virus loaded onto such a column is recovered. Two ml of a virus suspension is loaded onto the column and eluded by 20 ml of buffer, and eluates collected in two ml cuts. Practically all the virus is found in the fourth and fifth cuts, the recovery being sharply limited to these two cuts.

In contrast to this result, we have found in four successive experiments that an attenuated Type I polio strain gives an entirely different result, only 0.1 per cent to 5 per cent of the virus being recovered. The strain used in these experiments is the Liu, Schaeffer strain, which is the Type I strain used in Sabin's attenuated living polio vaccine. In other words, the attenuated strain differs from the neuro-virulent Mahoney strain in being much more avidly held by the ion-exchange column. This indicates a clear-cut physical difference between the two virus strains. The method described is very simple to carry out and could be adopted in any virus laboratory.

Therefore we believe the "DEAE" "marker" which we have discovered may be of great practical importance in selecting attenuated strains to be used in the manufacture of living poliovirus vaccines. We believe also that this "marker" will be of great value in the identification of virus excreted by human beings during large-scale field trials with such vaccines. Thus, it should be of great value in the early detection of the reversion of attenuated poliovirus strains to neuro-virulence, should such reversion occur.

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Important Notice

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THE JOURNAL OF
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The ability of glucagon to correct alimentary hyperlipemia is well established (29, 30, 95, 96). Destruction of the pancreatic alpha cells by cobaltous chloride (95) or by instillation of a potent staphylococcal toxin into the ligated pancreatic duct of dogs and rabbits (96) impairs glucagon production, causing serum lipids (particularly triglycerides) gradually to rise, with the ultimate development of lactescent serum. Albrink and Klatskin reject this effect as a likely source of hyperlipemia in acute pancreatitis, because of an apparent discrepancy in the rate of appearance of lipid response experimentally and clinically, the latter being the more rapid (88). Wang, Strauss, and Adlersberg, however, observed a rapid accumulation of lipids in serum one to four days after the production of pancreatic injury (96).

The role of calcium metabolism in pancreatitis is not yet clarified. Marked calcium deposition has been discovered in necrotic pancreatic and adipose tissue of patients with acute pancreatic necrosis without hyperlipemia (112). Presumably, the calcium was incorporated into soaps by the liberated fatty acids, and maintained in solution by neutral fat. This shift in calcium distribution apparently depleted serum calcium to subnormal levels (7–8.8 mgm per cent), with the production of hypocalcemic tetany, responsive to the intravenous administration of calcium salts. Tetany was also observed in two patients with acute pancreatitis and secondary hyperlipemia, whose serum calcium and pH values were normal (113). In these patients, tetany was unresponsive to parenteral calcium, but improved with the administration of parathyroid hormone or subsided spontaneously with the progressive decline in serum lipid levels. These latter cases suggest that NEFA may have preferentially combined with calcium, instead of albumin, with a consequent retardation in triglyceride clearance and reduction in serum ionizable calcium, thereby provoking hyperlipemia and normocalcemic tetany.

Liquefaction of fat has been visualized at the site of necrotic pancreatic and adipose tissue in acute pancreatitis (112, 114). It has, therefore, been postulated that blood vessel walls, damaged locally by pancreatic enzyme activity, permit entry of the digested interlobular and peripancreatic fat into the circulation. This probably enters in liquid form, since triglycerides and fatty acids, such as oleic acid, are fluid at body temperature (112). Once in circulation, fat embolism may occur, especially to the kidney and lung (88, 112, 114), but also in widely disseminated form (91). Since triglycerides have the same staining properties as the lipid found in areas of fat necrosis and in fat emboli, it has been inferred that adipose tissue injury is the probable origin of fat for embolization, rather than the free fatty acids released (88). This sequence of events has been considered as a possible explanation for the frequency with which fat embolism is seen in chronic alcoholics (115). Klatskin and Gordon noted sufficient elevation of pancreatic enzyme activity in some attacks of acute pancreatitis to produce *in vitro* clumping of chylomiera (91).

Fat embolization has often been attributed to a predisposition of blood to coagulate in the presence of hyperlipemia. Studies in alimentary hyperlipemia have repeatedly shown rapid clotting time of blood in silicone-coated tubes (116, 117), as well as shortened one-stage prothrombin times, utilizing Russell viper-

venom (stypven) as a fat-free thromboplastin (117, 118). These findings were later corroborated by Robinson and Poole who observed a marked increase in thrombin generation following the addition of rat chylomicra or one of several brain ethanolamine phosphatide preparations to plasma freed of particulate fat (119). Since ionophoresis and chromatography disclosed the presence of an ethanolamine-like component in acid hydrolyzates of chyle, they concluded that chylomicra probably potentiate rapid blood coagulation by the action of ethanolamine phosphatide.

Whether fat embolism is a result or a cause of pancreatitis in idiopathic hyperlipemia remains a matter of speculation, since hyperlipemia of any origin, primary or secondary, may be accompanied by fat embolization. Hyperlipemia could conceivably instigate pancreatitis by producing xanthomatous lesions in the pancreas, which might undergo spontaneous resolution by dietary fat restriction, and thereby escape pathologic detection. Or, perhaps, atherosclerotic plaques are formed in the pancreatic blood vessels which are capable of inducing an ischemic form of pancreatitis (91). This would seem unlikely, since neither the symptoms nor the histologic findings is consistent with a course of chronic arterial insufficiency.

In summary, it appears that acute pancreatitis may produce transient secondary hyperlipemia by a mechanism not well clarified at the present time. Several mechanisms are currently under scrutiny. Post-mortem studies in both human and experimentally-produced pancreatitis have revealed liquefaction of fat in necrotic adipose and pancreatic tissue, which may cross locally injured vascular walls, thereby elevating serum lipid levels to an abnormal range. Experimental destruction of pancreatic alpha cells may have a clinical counterpart, by which glucagon deficiency may interfere sufficiently with carbohydrate metabolism to produce hyperlipemia. Recent observations in patients with acute pancreatitis and hyperlipemia with concomitant tetany have suggested the possibility that both the rise in serum lipids and the clinical tetany may be the result of triglyceride binding with ionized calcium, rather than albumin, consequently reducing the efficiency of lipid transport.

In idiopathic hyperlipemia with relapsing pancreatitis, serum lipid values are always above normal, owing to a delay in lipid transport by unknown factors. In some instances, this delay appears to be related to a deficiency in lipoprotein lipase or, perhaps, to an excessive elaboration of a lipid-mobilizing hormone by the posterior pituitary gland. Since chronic pancreatitis may exist in an asymptomatic form, it is difficult to outline the proper sequence of alterations. Hyperlipemia probably precedes the development of pancreatic disease, since lipid abnormalities may be familial in many instances, suggesting an inborn error of metabolism (88, 120, 121). In addition, hyperlipemia may exist without any clinical evidence of pancreatitis, or may persist long after abdominal crises appear to have ceased (91). Cutaneous xanthomata may precede abdominal pain in an acute exacerbation, and both skin and abdominal symptoms may be at least partially controlled by regulation of serum lipid levels (88, 91). The suggested mechanisms by which idiopathic hyperlipemia may produce pancreatitis include

fat embolism or the production of xanthomatous or atherosclerotic lesions in the pancreas.

CLINICAL MANIFESTATIONS

The clinical syndrome of idiopathic hyperlipemia with relapsing pancreatitis is usually first manifest in childhood or early adult life, and appears predominantly in male Caucasians (90). A family history is present in a small proportion of the cases (88, 91, 104, 121, 122). Hyperlipemia is sustained in the intervals between abdominal crises. During crises, serum lactescence is frequently observed, and may be accompanied by cutaneous xanthomata and lipemia retinalis (69, 75, 88, 89, 90, 91, 92, 120). The xanthomata are usually eruptive, appearing first on extensor surfaces as yellow papules with inflammatory halos, and later becoming more diffuse (90). Xanthoma tuberosum is considerably more common than either xanthoma tendinosum or xanthelasma, in contrast to a reversed frequency seen in idiopathic hypercholesteremia (89). In lipemia retinalis, the retinal arteries and veins both appear salmon pink in color, with the latter sometimes containing a visible stream of fat droplets (90).

Hepatic or splenic enlargement may occur only during the acute episode or may be persistent (69, 75, 90, 92), may remain absent (121), or may not appear until hyperlipemia is long-standing (75).

A predisposition to atherosclerosis is apparent, with 34 per cent of Adlersberg's series manifesting coronary artery disease (89). Engelberg has attempted to correlate serum levels of cholesterol and low-density lipoproteins with abnormalities on ballistocardiography (123). The resting ballistocardiogram showed a tendency, most prominent below the age of fifty, for abnormalities to be associated with higher lipid values. A better correlation with serum lipids, at all ages, was observed with exercise, higher lipid levels being found when exercise intensified the ballistocardiographic abnormality and lower levels noted when the record improved after exercise.

In idiopathic hyperlipemia, transient cerebral manifestations were noted in 4.5 per cent and diabetes mellitus was found in 7 per cent of 48 patients (89). When idiopathic hyperlipemia, diabetes, and severe vascular disease coexisted, Adlersberg and Wang felt this constituted a separate clinical syndrome (120). This group of patients differed from those without diabetes by exhibiting a marked lability in the serum lipids, as well as aggravation of the underlying hyperlipemia by lack of diabetic control, even in the absence of ketosis (124). Treatment of both the diabetes and the hyperlipemia rarely brought the total lipid values to normal. In contrast, uncontrolled diabetes with secondary hyperlipemia is accompanied by ketosis, and generally produces a much less significant rise in serum lipids, which can be restored to normal by proper diabetic management alone.

Familial hyperlipemia is regarded by Wilkinson as a genetic predisposition, inherited as an incomplete dominant trait with little penetrance (122). Homozygosis produces both hyperlipemia and other clinical abnormalities, whereas the heterozygous state yields an individual with the lipid metabolic defect alone.

TREATMENT

Many therapeutic modalities have been utilized in an endeavor to regulate serum lipid levels. When control is achieved, even without quite reaching the normal range, many of the clinical manifestations will be arrested or held in abeyance for a duration of time exceeding the pretreatment course.

Rigid dietary restriction of fat, cholesterol, and calories has been successful in clearing serum lactescence by lowering serum lipids (75, 88, 91, 120). Selective limitation of dairy foods, coconut oil, and alcohol, however, has been reported to maintain a normal serum lipid concentration (125). Wilkinson prefers a regimen of spaced fat feeding, allowing postprandial hyperlipemia to subside prior to the next meal. This occurs within 24 hours in 75 per cent of his patients. Spacing of meals is gauged by the time required for an individual to clear his serum of a fat load after one or more months of equilibration (122). Intravenous neutral fat emulsion will decrease serum triglycerides and cholesterol, but is impractical for long-term maintenance therapy (80).

Administration of lecithin, choline, thyroxine, insulin, and liver extract (100), as well as blood transfusions (75, 100), is ineffective. Estrogen therapy combined with a low-fat diet, given for at least two months, will partially control serum lipids (126, 127). β -sitosterol interferes with cholesterol absorption from the gut and from bile, probably by competition with cholesterol for esterification. When given orally to patients with idiopathic hyperlipemia, a prolonged fall in serum cholesterol, triglycerides, and total lipids is only moderately well obtained, the effect on phospholipids being less marked (128). The use of oral chlorpromazine in dosages of 100-200 mgm daily has, in two patients, convincingly lowered all serum lipid fractions, particularly triglycerides, to near-normal levels, with a subsequent rise to the pretreatment range upon discontinuance of the drug (129).

The striking effect of heparin on acceleration of fat transport has stimulated extensive clinical trials in idiopathic hyperlipemia. A single injection of heparin causes a fall in all lipid components (129-131), as well as a shift in lipoproteins to the lower S_f classes (79). A continuous intravenous infusion in alimentary hyperlipemia returns the abnormal I^{131} -lipid tolerance curve to normal (58). One to two thousand I.U. of sublingual heparin clarifies postprandial hyperlipemic serum (132). Although sustained normal lipid levels are seldom obtained, heparin therapy represents an important adjunct to dietary management. Its usefulness will increase as the simpler routes of administration prove their merit with more protracted evaluation.

Observations by Altschul and his associates (133), later confirmed by others (134-137) indicated that nicotinic acid, in contrast to its amide, is a potent agent in depressing serum cholesterol levels in normal and hypercholesteremic individuals. Its mechanism of action is unknown. Application of nicotinic acid to patients with idiopathic hyperlipemia, in daily oral dosages of 3 Gm, maintained reduction of all serum lipid fractions, with cholesterol, triglyceride, and total lipid response exceeding that of phospholipids. Carbohydrate tolerance in non-diabetic individuals was also consistently and significantly diminished (138). As yet, no major side-effects have been reported.

Management of patients with idiopathic hyperlipemia is still imperfect. Dietary fat, cholesterol, and calorie restriction appears to be important. The supplementary administration of nicotinic acid, heparin, or ethinyl estradiol seems to enhance the effectiveness of dietary therapy, but frequently does not achieve the optimal sustained depression of serum lipids to normal levels.

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FAMILIAL DEFECT IN LIPID METABOLISM MASKED BY DIABETIC HYPERLIPEMIA

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INTRODUCTION

Biochemical abnormalities in lipid metabolism may occur in response to disorders of biliary, pancreatic, endocrine, or renal function. When the serum total lipid level exceeds 1 Gm per cent, and the predominant rise is in the triglyceride (neutral fat) fraction, serum lactescence may appear, and the resultant state is called hyperlipemia. When hyperlipemia is unassociated with any known causative factor, it is designated idiopathic, and represents a primary, inborn defect in circulating lipid clearance, whereby lipids are retained in the blood stream for grossly prolonged periods of time (1-3).

Idiopathic hyperlipemia is a familial condition apparently inherited as an incomplete dominant trait (4, 5). Some patients with this disorder have been found to be deficient in a specific tissue enzyme, lipoprotein lipase, which, when activated by heparin, is capable of accelerating the clearance of circulating lipids (6, 7). The recovery in plasma of a lipid mobilizing hormone released by the posterior pituitary gland has led to speculation that it may be present in excessive amounts in the hyperlipemic state (8, 9). Its mechanism of action is to stimulate the elaboration of triglycerides from adipose tissue into the circulation.

The carbohydrate metabolic defect in diabetes mellitus is accompanied by a retardation of fatty acid synthesis, accelerated ketogenesis, and excessive lipid mobilization from fat depots. When diabetes is uncontrolled, ketosis and hyperlipemia may result (1, 10-13). The biochemical deviations from normal fat metabolism in diabetes mellitus and idiopathic hyperlipemia, and the accompanying clinical characteristics, have recently been reviewed extensively (14).

When lactescent serum is found in a patient with uncontrolled diabetes mellitus, its origin is often difficult to discern, since it may reflect the presence of either diabetic hyperlipemia or idiopathic hyperlipemia or both. Although the principal immediate concern is the rapid regulation of the diabetic ketosis, the long-term management and prognosis depend heavily on the early recognition of an underlying lipid metabolic abnormality if one exists. To illustrate this problem, the following patient with idiopathic hyperlipemia, complicated by diabetic ketosis is presented.

CASE REPORT

A 41 year old white, American male diabetic entered The Mount Sinai Hospital because of diabetic ketosis and lactescent serum. The patient, a former prize-fighter, was known to have had diabetes mellitus of five years duration, controlled for the first four years by daily injections of 15 units of globin insulin, supplanted during the last year by 250 mgm

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TABLE I

Serial Lipid Determinations of the Patient's Fasting Serum, with Random Lipid Partition Studies of Fasting Serum from the Patient's Parents

Serum Analyzed	Date	Gross Appearance	Total Lipids (mgm %)	Phospholipids (mgm %)	Total Cholesterol (mgm %)	Cholesterol Esters (mgm %)	Triglycerides (mgm %)	Fasting Blood Sugar (mgm %)	Glycosuria (Clinitest)	Ketonuria
Patient	7-22-58	Lactescent	10,530	1,040	1,108	660	8,382	224	Variable	Present
Patient	7-26-58	Turbid	2,555	464	526	368	1,565	188	Variable	Absent
Patient	3-9-59	Slightly lactescent	2,620	436	462	289	1,722	167	3 ⁺ %	Absent
Patient's Mother	7-26-58	Turbid	1,605	400	367	265	838		None	Absent
Patient's Father	8-1-58	Clear	925	260	219	168	497		None	Absent

of tolbutamide each day. For several months, the patient had noted the presence of 2 to 4 plus glycosuria, as determined by clintest tablets. He related a two-month history of virtually constant, dull, pulsatile, occipital headaches, most severe around midnight, associated with polyuria, polydipsia, weakness, paresthesias of the right hand, and a papular skin eruption on the anterior thorax and lower extremities, which on occasion was pruritic. During the past month, the patient was aware of frequent flatulence and postprandial retrosternal burning, unrelieved by antacids, as well as mild recurrent calf pain on walking and infrequent palpitations of the heart. The patient's appetite was excellent, and his weight had remained stable. He denied any acute episode of abdominal pain in the past, diarrhea, previous exanthema, dyspnea, or anginal-type pain.

More than 20 years earlier, the patient had been treated for pneumonia and two cerebral concussions. Fifteen years previously, he contracted falciparum malaria in New Guinea, accompanied by alopecia universalis. Adequate atabrine therapy was administered, with no subsequent adverse sequelae. There was no knowledge of persistent splenomegaly.

The patient's mother is a known diabetic with coexistent idiopathic hyperlipemia. Under optimal diabetic control, her total serum lipids measured 1,605 mgm per cent, of which 52 per cent (838 mgm per cent) were triglycerides, the remaining lipid fractions also being elevated. The patient's father is a non-diabetic with essentially normal serum lipids in all fractions. His total lipid concentration was 925 mgm per cent, containing 53 per cent (497 mgm per cent) triglycerides (Table I).

The patient on physical examination appeared husky and somewhat obese. He was afebrile, with a ventricular rate of 80, and a blood pressure of 120/75. Generalized alopecia was evident. A skin eruption was present on the anterior chest and legs, consisting of small, discrete, non-pustular, yellow papules with a red base. Fundoscopic changes consistent with lipemia retinalis were observed in the absence of other retinal abnormalities. There was firm, non-tender hepatic and splenic enlargement, with the liver and spleen descending four cm and two cm beneath the right and left costal margins, respectively. Peripheral pulses were full. The only neurologic abnormality was a diminished vibratory sensation in the feet and ankles. The heart was slightly enlarged, with a normal third heart sound audible along the left sternal border. There was also moderate benign hypertrophy of the prostate.

At the time of admission, the patient's urine contained glucose in excess of two per cent, in association with ketone bodies. The blood was grossly creamy, and fasting blood sugar determinations ranged between 188 and 262 mgm per cent. Serum amylase was ten modified Somogyi units (normally 80-180). An erythrocyte sedimentation rate was 24 mm in one hour.

Serum sodium and chloride concentrations were markedly depressed while lactescence persisted (probably artifactual), but subsequently, the electrolyte levels returned to normal. The carbon dioxide content of the venous blood was 23.4 mEq/L. Thyroidal radioactive iodine uptake was 35 per cent of the administered dose in 24 hours. The electrocardiogram showed nonspecific ST segment and T wave changes. Abdominal roentgen films failed to disclose the presence of calcifications in the region of the pancreas. Serum protein studies revealed a mucoprotein level of 111 mgm per cent (normally 48-75), acid-precipitable globulin of 19.5 units (normally 4-8), and a zine sulfate turbidity of four units (normally 4-8). This was interpreted to indicate high α_1 globulin and α_2 plus β -globulins, with a relatively low gamma globulin, a combination compatible with hyperlipoproteinemia.

Total serum lipids were 10,530 mgm per cent, with 8,382 mgm per cent triglycerides, 1,040 mgm per cent phospholipids, and 1,108 mgm per cent cholesterol, of which 660 mgm per cent was esterified (Table 1).

The patient was immediately started on 65 to 75 units of NPH insulin daily and a low fat, low calorie diet. After three days had elapsed, the ketosis had subsided, but varying quantities of glycosuria persisted. By this time, fasting serum lipid values had declined to a total concentration of 2,555 mgm per cent of which 1,565 mgm per cent represented triglycerides, 464 mgm per cent phospholipids, and 526 mgm per cent cholesterol, with 368 mgm per cent cholesterol esters. Within a few more days, the eruptive xanthomata and lipemia retinalis had disappeared, and the liver had receded somewhat in size. By the twelfth day, the patient was aglycosuric, and left the hospital against advice.

Seven and one-half months later, after continued diabetic therapy, the patient's serum again appeared lactescent. At this time, a fasting blood sugar level was 167 mgm per cent, associated with considerable glycosuria and no ketonuria. Total serum lipids were 2,620 mgm per cent, containing 1,722 mgm per cent triglycerides, 436 mgm per cent phospholipids, and 462 mgm per cent cholesterol, of which 289 mgm per cent was esterified (Table 1).

DISCUSSION

The combination of historical features, physical findings, and therapeutic response to a diabetic regimen serves to differentiate diabetic from idiopathic hyperlipemia. In diabetes mellitus, lactescent serum is seen only in the presence of hyperglycemia and ketosis, with rare exceptions, and usually without any characteristic changes in physical appearance. Hepatomegaly may be present, however, but its onset does not typically coincide with the development of hyperlipemia. Following adequate treatment of the diabetic ketosis, the serum lipid levels return fairly rapidly to normal as the ketonemia disappears (10, 12). Although diabetes frequently is familial, diabetic hyperlipemia is not present in well regulated diabetic relatives.

In contrast to the diabetic with secondary hyperlipemia, the patient with idiopathic hyperlipemia may have a preceding history of serum lactescence. There is occasionally a familial incidence of hyperlipemia. Frequently, the patient describes recurrent attacks of acute abdominal pain, which usually represent a chronic, relapsing pancreatitis (1, 4, 15, 16). Often there is hepatic and splenic enlargement (17, 18), eruptive xanthomatosis (18, 19), and lipemia retinalis (18). Not infrequently, xanthoma tuberosum is present (15). When the serum lipid level in idiopathic hyperlipemia is augmented by diabetic hyperlipemia, the latter component usually responds well to insulin therapy. However, serum lipid levels (all fractions) remain somewhat elevated, even with dietary fat restriction.

When idiopathic hyperlipemia is accompanied by diabetes mellitus and severe vascular disease, the serum lipid level fluctuates widely, and may be markedly exaggerated by lack of diabetic control, even without ketosis. Treatment of the hyperlipemia in these patients is generally unsatisfactory. The different behavior of these individuals led Adlersberg and Wang to classify this combination of findings as a distinct syndrome (20).

Although appropriate regulation of diabetes mellitus may minimize the incidence of premature atherosclerosis, if idiopathic hyperlipemia in the same patient remains untreated, the same predisposition to coronary heart disease exists (15). Chiefly for this reason, correction of the primary lipid defect must be attempted. Although maintenance of a normal serum lipid level is seldom achieved, the most favorable response follows the institution of a low fat, low calorie diet, supplemented by an antilipemic drug, particularly heparin (21-23), nicotinic acid (24, 25), or ethinyl estradiol (26).

The patient described emphasizes the difficulty in evaluating hyperlipemia in a diabetic. Lactescent serum remained undiscovered until lack of diabetic control imposed an additional embarrassment on the already abnormal fat metabolism. As serum lipids rose to remarkable heights, there appeared the typical clinical manifestations of hyperlipemia: eruptive xanthomatosis, lipemia retinalis, and hepatosplenomegaly. (The role that the previous malaria played in the current enlargement of the spleen is undetermined). Relapsing pancreatitis is not an essential feature for diagnostic confirmation. In spite of the low serum amylase determination, there is no clinical evidence in this patient, other than diabetes mellitus, to suggest chronic pancreatic insufficiency. Treatment of the diabetic ketosis presumably ameliorated only that increment of hyperlipemia to which ketosis contributed, without restoring lipid levels to normal. It is to be anticipated that the therapy instituted would not be capable of sustaining normality in lipid concentration of the blood. The apparent lability and rapid fluctuations in the patient's serum lipids suggest that, even in the absence of advanced vascular insufficiency, this patient may well represent an early example of the syndrome described by Adlersberg and Wang (20). The therapeutic approach toward this patient must be one of combined diabetic regulation and dietary measures aimed at maintaining low serum lipid levels. The latter might most readily be accomplished by the supplementary use of antilipemic agents.

SUMMARY

A case of idiopathic familial hyperlipemia in a 41 year-old white male diabetic is presented. Failure to adequately control the patient's diabetes resulted in the development of ketosis, accompanied by serum lactescence with enormous elevation in the serum triglycerides, eruptive xanthomata, lipemia retinalis, and hepatosplenomegaly. All the clinical manifestations of this condition responded satisfactorily to the restoration of diabetic control and maintenance of a restricted fat intake, with the exception that all fractions of the serum lipids failed

to return to normal, but only to a level where frank lactescence disappeared. The clinical findings and course of events serve to differentiate the underlying metabolic abnormality from diabetes mellitus with secondary hyperlipemia.

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DIAGNOSTIC CONIZATION OF THE UTERINE CERVIX IN PREGNANCY

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The diagnosis of carcinoma *in situ* of the cervix during pregnancy has usually been suspected on the basis of abnormal cytologic smears, to be confirmed ordinarily by multiple punch biopsies. Because of the frequent difficulty in differentiating physiologic pregnancy changes of the cervical epithelium from neoplastic changes, many pathologists have been reluctant to make a definite diagnosis of carcinoma *in situ* at this time. Cold knife conization of the uterine cervix in pregnancy has only rarely been utilized as a diagnostic aid. This report has two objectives: First, to emphasize that the microscopic diagnosis of pre-invasive carcinoma of the uterine cervix can and should be made during pregnancy and the methods of obtaining tissue for study should be the same as in the non-pregnant state. Second, to illustrate in a case report a technique by which cold knife conization of the cervix during pregnancy may be rendered feasible and safe for mother and fetus.

The uterine cervix undergoes alteration during pregnancy (1). It becomes edematous and very vascular. One may find a decidual reaction in the stroma and there is often eversion of the cylindrical endocervical epithelium with secondary inflammatory changes. The endocervical canal becomes the site of reserve cell proliferation and squamous metaplasia. The stratified squamous epithelium of the ectocervix becomes thicker, and responds to the endocervical eversion by epidermidizing these areas. Basal cell hyperplasia, the most important and controversial histologic change, is found in 10 to 20 per cent of pregnant cervixes (1-3). This lesion may arise in the endocervix as a product of reserve cell hyperplasia, and occurs somewhat less frequently in the basal layers of the ectocervix and in areas of epidermidization. The true site of origin is often impossible to determine. A majority of these hyperplastic epithelial alterations will revert to normal within six months after delivery (1-4). Lesions that have not disappeared by this time tend to persist and even progress. The degree of hyperplasia in pregnancy can be marked, and there may be some cellular atypism and incomplete loss of epithelial stratification. Some of these anaplastic changes will produce suspicious cytologic smears (5). The cases of basal cell hyperplasia with more atypism are less likely to revert to normal (3, 6).

Many cases of basal cell hyperplasia are not limited or even related to pregnancy, but represent coincidental findings (4, 6, 7). Their incidence and rate of reversion are the same, irrespective of pregnancy. Persistent cases of atypical hyperplasia are of great importance, for they may be coexistent with preinvasive carcinoma or eventually progress thereto (5, 8). The finding of basal cell hyper-

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plasia with degrees of atypism should not be regarded lightly at any time. The patient exhibiting this lesion deserves diagnostic conization of the cervix and careful follow-up. Hellman suggested that epithelial dysplasias arising in the endocervix are usually reversible and directly related to the pregnancy, although identical changes may be produced in this area by unopposed estrogen stimulation, infection, and trauma (1). He considers the atypical hyperplastic changes in the ectocervix in a different category, independent of pregnancy or hormonal stimulation and less often reversible. There is no agreement as to whether the endocervical or ectocervical lesion is more significantly related to subsequent carcinoma, although invasive carcinoma in general probably originates more often in the cervical canal than on the ectocervix.

The epithelial changes in the cervix during pregnancy have on occasion obscured the histologic criteria for the diagnosis of carcinoma *in situ*. There has been a tendency on the part of many observers to procrastinate with a suspicious lesion into the puerperium, and to make a definite diagnosis of carcinoma *in situ* only in persistent lesions. Greene and Peckham (9), Marsh and Fitzgerald (10), and Carter (11) have objected to this indecisive approach. These authors feel strongly that a definite diagnosis can and should be made during pregnancy. Greene and Peckham do not require complete loss of stratification as one of the diagnostic criteria, but do insist on nuclear abnormalities in all layers (9).

Cervical cytology, as well as histology, reflects the cellular changes occurring in the ecto- and endocervix during pregnancy, and there has been similar hesitation in making an absolute interpretation of Papanicolaou smears taken at this time. With increasing experience, longer follow-up studies, and a growing understanding of the histologic changes of pregnancy, greater certainty has been achieved in the evaluation of cytologic smears taken during gestation. Nieburgs and Clyman state that during pregnancy "only the parabasal cell dyskaryosis, if associated with marked hyperchromasia, is considered an adequate cytologic basis for a suggestive interpretation of carcinoma *in situ*" (12). Today cervical cytology is considered an important and reliable screening technique and guide in the detection of atypical and malignant cervical lesions during pregnancy (5, 13-15).

The entity of carcinoma *in situ* of the cervix is the same, irrespective of pregnancy. It has the same incidence, approximately 0.5 per cent, in both pregnant and non-pregnant women and does not seem to be influenced in any way by one or more pregnancies (5, 11, 13). Evidence is accumulating that true carcinoma *in situ* is an irreversible lesion (2, 9-11, 13). A resume of the reported cases of carcinoma *in situ* diagnosed during pregnancy and followed for at least six months postpartum shows that approximately 80 per cent of the lesions persisted. The "disappearance" of one fifth of these lesions has been explained on the basis of either complete removal at the time of original biopsy or incorrect interpretation of the pathologic changes at that time. Greene and Peckham pointed out that the same rate of "disappearance" existed in those cases of preinvasive carcinoma diagnosed and followed in the non-pregnant state, and probably for the same reasons (9).

The diagnostic problem in the non-pregnant patient is to rule out invasive carcinoma of the cervix. Carcinoma *in situ* is often found in the surface epithelium immediately adjacent to areas of invasive carcinoma (5, 8). Cold knife conization of the cervix may find evidence of this invasion not revealed by multiple punch biopsies. This diagnostic error in one large series was 3.6 per cent (9), and in another analysis 7.5 per cent (15). There is every reason to assume that at least the same percentage of error will obtain during pregnancy. Yet cervical conization to rule out invasion has rarely been performed in the parturient. An incomplete diagnosis, based on a reluctance to perform cold knife conization of the cervix in pregnancy, carries an overwhelming risk for the patient. Whereas the five year survival rate of patients with invasive squamous cell carcinoma of the cervix treated prior to the 34th week of gestation does not differ appreciably from that of the non-pregnant state when compared stage for stage, this rate drops to less than 25 per cent when the diagnosis is made or treatment deferred to term or the puerperium (16, 17). It is obvious that a secure diagnosis of carcinoma *in situ* during pregnancy is imperative, and therefore cervical conization must not be deferred to the postpartum period if it can be carried out safely.

CASE REPORT

A. R. (MSH # 142287), a 43 year old Puerto Rican gravida 3, para 2-0-0-2, was first seen in the Prenatal Clinic of The Mount Sinai Hospital in January, 1960. The expected date of confinement was June 23, 1960. Her last delivery had been in 1938. Menstrual periods had been regular, with no intermenstrual or post-coital spotting. The history and physical examination were within normal limits; the cervix was unremarkable on inspection. Routine cervical cytologic smears were taken, and reported as showing large numbers of cells with changes suggestive of atypical hyperplasia. Repeat smears one month later again showed marked atypical hyperplasia. Accordingly, the patient was admitted to the hospital in the 26th week of gestation for further diagnostic procedures.

In the operating room, under general anesthesia, the patient was placed in the lithotomy position and the cervix visualized and painted with Lugol's solution. Five punch biopsies were taken around the circumference of the squamocolumnar junction. Bleeding from the biopsy sites was brisk, and figure-of-eight chromic catgut sutures were necessary to secure hemostasis at each site. The estimated blood loss was approximately 400 cc, and the patient required one unit of blood to restore the blood pressure which had dropped. The post-operative course was benign. Pathologic examination showed scattered areas of excessive squamous cell epithelial proliferation; in one area there was marked cell atypism and many mitoses throughout all layers. No infiltration could be found. The interpretation was that of carcinoma *in situ*.

Further cytologic studies of the cervix continued to show grossly abnormal cellular morphology. In the 32nd week of gestation, when the baby was considered to be fully viable, the patient was readmitted to the hospital for conization of the cervix.

In the operating room, under general anesthesia, the cervix was exposed and grasped in four quadrants with Allis clamps. Inspection revealed that the portio vaginalis of the cervix was three centimeters long, the external os two centimeters dilated, and the internal os closed. A #5 braided surgical silk suture was passed submucosally as a purse-string at the junction of the rugose vagina with the smooth portio vaginalis of the cervix. The bladder was not advanced, nor was any attempt made to reach the level of the internal os. The suture was not fixed to the cervical substance, and was tied with only moderate tension to avoid cutting through the edematous tissues. A cold knife conization of the squamocolumnar junction and the distal three fourths of the endocervix was then accomplished with

ease; the apex of the cone reached the level of the purse string suture. Bleeding, in contrast to the previous procedure, was negligible. Four Sturmdorf-like sutures of #0 chromic catgut were placed in the four quadrants of the cervix, both to control slight oozing from the mucosal edges and to reconstruct the cervix. Neither vaginal packing nor vasoconstricting solutions were utilized. The patient's postoperative course was uneventful; there was no vaginal bleeding, onset of uterine contractions, or pyrexia. The microscopic pathology of the conization specimen again revealed preinvasive carcinoma.

Subsequent cytologic studies of the cervix consistently demonstrated only "slight epithelial dysplasia". In the 38th week of gestation, the patient entered the hospital in early labor. Under spinal anesthesia, a female infant in good condition weighing 3940 Gm was delivered by classical cesarean section. As part of the same procedure, a total abdominal hysterectomy including a cuff of vagina and a right salpingo-oophorectomy were performed. The patient had an uneventful postoperative course.

The microscopic pathology of the surgical specimen revealed residual preinvasive carcinoma high in the cervical canal. In addition, one focal area in this region showed superficial infiltration of malignant cells. Because of the now altered microscopic diagnosis, the patient received external radiation to the pelvis.

DISCUSSION

Conization of the uterine cervix in pregnancy has four practical hazards and one theoretical objection. The hazards are: hemorrhage, onset of labor, secondary cervical incompetence resulting in pregnancy wastage, and rupture of the amniotic sac during the procedure. The theoretical objection concerns the removal of the entire diseased portion of the cervix by conization, which prevents follow-up with respect to possible regression. This latter objection becomes less valid the more experience indicates that definitive diagnoses of carcinoma *in situ* can be made during pregnancy on histologic criteria and without demonstrating persistence of the lesion postpartum.

There have been isolated reports of cold knife conization performed during pregnancy. Greene and Peckham (9) reported conization in five pregnant patients, but did not specify technique or discuss complications of the procedure. Schmitz and his co-workers (5, 18) have carried out cervical conization over a period of years in cases where preinvasive carcinoma has been diagnosed by multiple punch biopsies. These authors insist that a diagnosis of carcinoma *in situ* cannot be established safely without adequate cone material. The total number of pregnant cases coned is not reported, nor was technique discussed; with respect to complications, they stated only that conizations were not responsible for any interruption of pregnancy (5). There was no obvious reluctance to perform this procedure, one conization being executed as late as the 35th week of gestation, and five cases of invasive cervical carcinoma were discovered in this way. Carter simply mentioned that in his experience with cervical conization in pregnancy abortion and premature labor were not encountered (11). Ferguson and Cavanagh (14) and Offen and Ferguson (19), reporting on the same series of cases, have performed conizations during pregnancy from the 8th to the 38th week. Their technique involves injection into the cervix of large volumes of vasoconstricting solution, use of a suction cautery, lateral cervical sutures for both hemostasis and traction, and postoperative packing of the defect. However, the hemostatic effects of the combined technique in pregnancy as compared to

the nonpregnant state "are not quite as dramatic, and a larger blood loss may be anticipated." At the time of the initial report, seven of the ten vaginal deliveries following this procedure had been premature. Beecham and Andros carried out cervical conization during pregnancy with the aid of a submucosal purse string suture similar to the one suggested in this report (20). The suture material employed was absorbable #1 chromic catgut, so that the suture was intended solely for purposes of hemostasis. These authors found two cases of invasive carcinoma in over two dozen patients coned, but the procedure was often performed on the basis of positive cytologic changes and without prior punch biopsies. Vaginal delivery was permitted in all cases except those with invasive carcinoma; one patient coned in the 36th week of gestation delivered uneventfully 48 hours later. Scott and co-workers described a technique for cervical conization whereby an "intracervical tourniquet" is produced by the injection of a saline-adrenalin solution into the cervical stroma, followed by coagulation of the defect (21). Conization by this method has been performed in all trimesters of pregnancy "without a single pregnancy loss." Finally, Stander and Lein indicated that they have utilized cervical conization during pregnancy and cite their prerequisites for the procedure (22).

Much experience has accumulated in our department in the use of the submucosal purse string (or Shirodkar) suture for correction of incompetence of the internal os of the cervix during pregnancy (23, 24). The procedure is simple and quickly executed. It was noted on repeated occasions that bleeding, encountered in varying amounts in the initial steps of the Shirodkar procedure, was immediately controlled once the purse string suture was placed and tied. It seemed that this type of suture might obviate or minimize all of the practical hazards encountered in cold knife conization of the pregnant cervix. By compressing the deep blood supply, relatively good hemostasis might be provided in the distal portion of the cervix. Application of the suture has never induced premature labor in our hands; to the contrary, increasing the cervical resistance in this manner was effective in some cases in minimizing the effects of an irritable uterus. The Shirodkar suture, specifically intended to treat cervical incompetence, would prevent secondary incompetence and pregnancy wastage. Finally, the constricting effect of the suture, placed just below the internal os of the cervix, would provide a protective barrier to accidental nicking of the amniotic sac during the procedure. From this reasoning, it appears that a Shirodkar purse string suture passed around the cervix prior to conization should make the procedure simple and safe for both mother and fetus.

Several details are of importance. The suture material employed must be of a permanent, non-absorbable nature in order to derive not only the short term advantages of hemostasis and protection of the amniotic sac, but the long term benefits of protection against cervical os incompetence and premature labor. The precise manner of passing this suture has been extensively described elsewhere; we feel that superficial placement of the suture is important to provide a safety factor against severe cervical lacerations or rupture of the lower uterine segment if labor should supervene before the suture can be removed (23). Vaginal

and cervical packing should be avoided, since they might stimulate uterine contractions; additional hemostasis, if necessary, should be achieved with catgut sutures used in the conventional manner.

The level at which the purse string suture is placed about the cervix will depend on how high the cone is intended to reach. In non-pregnant patients, the internal os is not reached in many conization procedures; the residual area of endocervix is often curetted at the same sitting (15). In the gravid patient, the level reached by cervical conization has not been specified in the reports cited above. We feel that extending the cone to the internal os or curetting the proximal portion of endocervix in a pregnant uterus imposes a great risk on the incumbent pregnancy, namely inadvertent amniotomy. Therefore, passing the Shirodkar suture at the level where the rugose vagina meets the smooth portio vaginalis, without mobilization of the bladder, permits excision of the distal three-fourths of the endocervical canal.

Conization in the non-gravid state is subject to some error and incompleteness (15). During pregnancy, the procedure may be even less reliable. To obviate the situation developed in the case report, it is suggested that all patients shown by cervical conization during pregnancy to have carcinoma *in situ* be delivered by cesarean section near term but prior to the onset of labor. Definitive treatment should await the results of a more complete diagnostic conization after the puerperium.

SUMMARY

A. The microscopic diagnosis of carcinoma *in situ* of the uterine cervix can and should be made during pregnancy.

B. Failure to diagnose and treat invasive carcinoma of the cervix before the 34th week of pregnancy materially worsens the patient's prognosis.

C. The only relatively certain means of ruling out invasive carcinoma is microscopic study of tissue obtained by cold knife conization of the cervix; this must be performed irrespective of pregnancy or the stage thereof.

D. The indication for diagnostic conization of the uterine cervix during pregnancy is the finding of basal cell hyperplasia with cellular atypism or pre-invasive carcinoma on punch biopsy. Conization should not be carried out without prior cervical biopsy.

E. A technique to minimize the dangers inherent in cervical conization during pregnancy is described.

F. The diagnostic limitations of the conization procedure during pregnancy are discussed.

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A PSYCHOLOGICAL ANALYSIS OF APPARENT DEPRESSION FOLLOWING RAUWOLFIA THERAPY*

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INTRODUCTION

In the past three years there have been many reports of depressive reactions in patients following the administration of the Rauwolfia preparations (1-6). Such reactions have constituted a major contra-indication to a full utilization of these compounds in the treatment of many illnesses. In this study, an attempt was made to establish objective criteria for the predication of depression in those patients prone to respond in this manner to the Rauwolfia drugs.

MATERIALS AND METHODS OF INVESTIGATION

Fifty consecutive patients from the Hypertension Clinic and Dermatology Clinic were the subjects of this investigation. These patients were studied by means of psychological tests, autonomic reactivity, and psychiatric interviews before, during and after the administration of the Rauwolfia compounds. The psychological tests included the Rorschach, Thematic Apperception, Bellevue-Wechsler, and Figure Drawings. The epinephrine-mecholyl test (Funkenstein Test), a sensitive indicator of autonomic reactivity, was utilized in an attempt to determine whether patients receiving Rauwolfia fall into predictable categories of depressive potential (7-10). The psychiatric interviews emphasized the present mental status, the past history, the psychodynamics, and the current adaptational maneuvers of the patient. Special attention was given to any disturbance of motor activity, mood, ideational content, and socialization.

The subjects consisted of 26 males and 24 females who were predominantly in the 40 to 55 year age group. Forty per cent of the group were of socio-economically deprived Puerto Rican and Negro origin, who were however within the average range of intelligence. The patients comprising the other sixty per cent of the group fell into similar categories of socio-economic and intellectual status. Nearly every patient was or had been married. Patients in the hypertensive group were chiefly in the early phase of their physical illness (six months duration), while the patients in the dermatological group were chiefly in the chronic phase of their physical illness (three to five years duration).

Two drugs were used. Raudixin® was administered to 47 patients with a daily oral dosage of from 50 to 400 mgm. Three patients received from 1 to 5 mgm of Serpasil® by mouth every day.

All patients were followed for twelve to eighteen months while the drug was

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being taken. Multiple base-line studies were performed on each patient. In addition to the initial psychological test batteries, psychiatric interviews and autonomic tests, all patients received a complete medical work-up including electrocardiogram, chest x-ray, and liver function tests. They were then seen once weekly by the psychiatrist and were subjected to two or more autonomic tests as well as one or more psychological tests during this study.

The psychologists and psychiatrist independently, on the basis of their findings, placed the patients into three groups. There were only three cases in which the psychologists and psychiatrist differed as to the depressive potential of the patient, and this was only a question of degree; *i.e.* high potential versus moderate potential. The three groups were as follows:

Group I: Those patients with a high potential for developing a depression: 11 patients.

Group II: Those patients with a moderate potential for developing a depression: 15 patients.

Group III: Those patients with a low potential for developing a depression: 24 patients.

The predictive criteria used were the following:

(a) Indications in the past history of any previous depression. (b) Indications of disturbance in mood, psychomotor activity, or intellectual functioning. (c) Indications of a chronic sense of guilt associated with unfulfilled aspirations, ambitions, or obligations. (d) Indications of the presence of an intensely ambivalent attitude toward some love object, coupled with a powerful emotional dependence upon this love object. (e) Indications of a sense of total rejection and abandonment at the hands of the social environment. (f) Indications of a sense of frustration or despair in the face of shrinking personal horizons and diminishing physical capacities. (g) Those patients who responded with a Group VI or VII reaction to the Funkenstein Test were weighted toward the hypothesized depression-vulnerable group. Our feeling was that since most patients who have a depression and respond well to electroshock fall into this group; these patients might be already autonomically primed for a depression, without its clinical manifestations.

RESULTS

The psychological test findings and the clinical interviews revealed the following predominant emotional pattern in the hypertensive group (26 patients). There was a minimum of overt phobic, hysterical, or obsessional neurosis. The patients were characterized by obsessive character traits and were reserved, conventional, and perfectionistic. Thirty per cent disclosed psychotic trends or their potential.

These patients manifested an overt facade of adequacy and self-reliance, but conscious feelings of inferiority and inadequacy were also present. There was an absolute minimum of acting out and aggressive outbursts in this group, with the exception of one patient.

Generally, these patients were overtly adequate as parents, but they derived minimal pleasure from their parenthood. Heterosexual activity was also adequate, but again there was a minimal pleasure. Although these patients had moderate intellectual, vocational, and social strivings, there were frequent failures in the attainment of these aspirations.

The general psychodynamic pattern of this group of hypertensive patients was their marked need for status, security, affection, and dependence. Unconscious rage, generated by the frustration of these needs, tended to be continuous rather than periodic. These patients had a great deal of difficulty in handling and expressing their anger, a problem existent since early childhood. The expression of anger seemed to carry with it a great risk—loss of maternal love and its derivatives, namely, affection, security, approbation, and prestige. In order to retain this affection and approbation, they have developed the technique of placation so as to preclude any possibility of jeopardizing their standing in the eyes of people upon whom they are dependent. A typical comment made by a patient when asked to describe himself was "I am easy to get along with. It has to be real hard for someone to get me angry." When asked what might get him angry, he replied, "If someone hits me." Another striking defensive maneuver was *activity*. Many of these patients had several jobs and found it difficult to relax. "I'm always happiest when I'm doing something anything," was another typical comment. It should be noted that this was basically a pattern of psychomotor activity and not reactivity to their environment.

The 24 patients in the group with skin disorders were characterized by general overt timidity and passivity. In contrast to the hypertensive group they showed more anxiety, more overt hysterical and obsessive features with greater inhibition in assertive and aggressive areas. They had much closer familial and environmental ties and demonstrated minimal adequacy in marital, parental, and vocational areas. Although these patients also had infantile dependency needs, anxiety was the predominant affect rather than rage. They were particularly prone to panic in relation to participation in adult sexual, marital, and parental activities. Guilty-fear and expiatory activity was also a predominant dynamic pattern in this group. Psychomotor activity as a defensive maneuver was rarely utilized by this group of patients.

Another feature of our series of patients was that eight subjects had previous histories of depression requiring psychiatric help, and two of these patients received electroshock treatment. None of these patients were excluded from this study, although they were classified at the time of observation as having subclinical, if not overt depressions.

The hypertensive and dermatological groups fell into all of the six groups of autonomic responsiveness as enumerated by the Funkenstein Test. There was no predominant grouping except for a slight propensity for Groups VI and VII on the initial testing. This is the grouping in which most depressed patients respond autonomically.

Group I	8 patients
Groups II and III	13 patients
Group IV	7 patients
Group V	4 patients
Group VI	14 patients
Group VII	4 patients

Although our patients were predominantly between the ages of 40 and 60, the time of life when statistically most depressions occur, *not one case of true depression* occurred in our series; (using as criteria of the depressive syndrome the three basic components of (a) dejected, apathetic mood, (b) slowing down in thinking, and (c) the inhibition of instinct and will). None of our patients became excessively self-deprecatory, suicidal, troubled by morbid thoughts or feelings of being "blue", "low", or weeping. There were few complaints of anorexia, weight loss, insomnia, constipation, or early morning awakening.

Twelve patients responded with a "pseudo-depression", a reaction of excessive tranquilization, with diminished *psychomotor activity* as the chief symptom. They complained principally of being "slowed down," "tired," and "lacking push," while on the drug. Eleven of these twelve patients were from the hypertensive group. The drug seemed to cause a retardation of the excessive psychomotor activity, which in these patients had become an important and habitual pattern of adaptation. Repeat psychological tests and clinical interviews gave no indication of a true depression in this group. When the dosage level of the drug was readjusted so that the patients were not "over-tranquillized," their complaints disappeared. In no case was it necessary to eliminate the administration of Rauwolfia to these patients. Again, it seems worthwhile to note that in the dermatological group of patients, where excessive psychomotor activity was not a predominant pattern, there was only one case of over-tranquilization; (a patient who was given an exceedingly high dose of Serpasil[®], 5 mgm O.D.).

In reviewing the psychological test batteries after the study was completed, the following points emerged:

(a) There were 14 patients from the hypertensive group in whom excess psychomotor activity was mentioned as an important defensive reaction. Every one of the 11 patients who responded with a "pseudo-depression" was in this group.

(b) There was one patient from the dermatological group with this defense, but he did not respond with an "over-tranquilization" reaction.

(c) In regard to the Funkenstein Test, 16 of our patients shifted into Group VI and VII, the group where depressives usually fall. Since the Rauwolfia compounds are adrenolytic agents, this shift was not unexpected (11-12). It would appear that something else is necessary, in addition to the shift of autonomic reactivity, to create a depression. (The relationship of autonomic reactivity and depression has been explained earlier in greater detail (13-15).)

(d) Our preliminary predictions of patients prone to respond to these drugs with a depression, or "pseudo-depression," showed very little correlation with

our findings. Only 3 of the 12 patients responding with a "pseudo-depression" were put in the "high potential" group prior to being given the drug.

SUMMARY

It is of course very easy to theorize from little data; in our case only fifty patients were followed for twelve to eighteen months. Depressive reactions, reported in the literature, might have occurred in a larger series of patients, or if they had been observed longer. Within these limitations however, our data suggest the following theoretical formulations:

(A) The Rauwolfia compounds do not appear to be a causal agent in bringing about the "depressive" reactions which have been encountered in their use. It is felt that the untoward reactions have nothing to do with the physiological effects of the drug *per se*, but rather with the way in which the physiological effects psychologically threaten the patient. The patient who appears to be most prone to develop a "pseudo-depressive" reaction to these compounds is the individual who feels threatened by being calmed, made less active, becoming tired or weak, who tends to use psychomotor activity as a means of reassuring himself that he is adequate, and who fears passivity. Under the influence of the enforced relative passivity physiologically produced by these drugs, the patient may react with anxiety or a "pseudo-depression". In essence, this chemical interference with the patient's defenses, imperfect though it may be, without substitution of something more useful to the patient, tends to disrupt the patient's previous adjustments.

(B) In our series there were five cases of overt depression treated with Rauwolfia compounds. In three cases, their agitation was controlled; in the other two cases, the symptomatology was not exacerbated. Again, this is further evidence to support the thesis that these drugs are not truly depressogenic.

(C) The Funkenstein Test does not appear to be of value in correlating shifts of autonomic reactivity with changes in clinical symptomatology in these instances.

(D) Our findings raise the question of the relationship of Rauwolfia drugs and depressions; *causal or coincidental*. It is our hope that this paper will stimulate further careful investigation into this problem.

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Clinico-Pathological Conference

DIABETES AND COUGH WITH NEURITIS AND GANGRENE

Edited by

FENTON SCHAFFNER, M.D.

A 72 year old white retired peddler was admitted to The Mount Sinai Hospital because of weakness and pains in his extremities for several months. Ten years earlier he had been said to have diabetes mellitus and x-rays then showed densities in both lung fields, more on the left. He had a cough productive of mucoid and mucopurulent sputum and numerous episodes of hemoptysis over a period of several years. In addition he had wheezing and dyspnea on exertion for many years. Two years later he developed mild arthritis in his extremities and back, for which he received small doses of steroids intermittently. Several months before admission he developed weakness of both lower extremities and both hands with muscle wasting, 20-pound weight loss, some swelling of his hand and foot joints and numbness. The numbness was likened to standing on cotton. The patient also dropped things because he could not feel them. He became so weak he was confined to bed.

Six days before admission to this hospital, he entered another hospital because he was unable to raise either foot and he fell when he tried to stand. Sphincteric function was intact. The patient was very depressed and cried easily. He had been depressed in the past and had attempted suicide twice several years earlier. The skin of his legs had been treated with x-ray therapy about two years prior to admission because of ulcerations on the sides of his legs. The physical findings and laboratory test results were the same as obtained later in this hospital. He was transferred here for further evaluation.

On examination his temperature was 100.2° with a normal pulse and blood pressure. He was poorly nourished and his tongue was smooth and reddened. The AP diameter of his chest was increased and fine crackling rales were heard in the left lower lung field. Expiratory wheezes were heard bilaterally. Heart sounds were normal. The liver was felt two fingerbreadths below the right costal margin and was slightly tender. A firm spleen tip was felt. Testicular atrophy, poor rectal sphincter tone and smooth enlargement of the prostate were noted. Deforming arthritis of the hands was present with pain on motion of the shoulders and elbow. Motion of the neck was also limited. The small muscles of both hands and lower extremities were wasted and a bilateral foot drop was present. Hypesthesia and diminished proprioception, thermal and vibratory sensation were noted in all four extremities. No fasciculations or abnormal reflexes were found. The left calf had some hemorrhagic scaling skin lesions with sharp and elevated borders.

Chest x-ray showed interstitial infiltrations in both lungs, which were emphysematous. The left costophrenic angle was blunted due to thickened

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pleura. Rounded lucencies were seen in each lung and were thought to be bullae. The heart was not enlarged and the aorta was tortuous. Review of serial films indicated that little change had occurred in ten years. Electrocardiographic changes were nonspecific and included atrial premature contractions, ST depressions and diphasic or low T waves in 2, 3 and AVF, T waves were also diphasic or low across the entire precordium.

Throughout the hospital stay the hemoglobin ranged between 11.2 Gm per cent to 10.1 Gm per cent and the white count between 7,000 per cu mm to 9,000 per cu mm except for one count of 18,000 per cu mm two weeks before death. Differential counts were all normal and averaged about 65 per cent segmented leukocytes, 20 per cent band forms, 12 per cent lymphocytes and the rest monocytes or eosinophiles. Sedimentation rate was 86 mm hr, twice. Many blood cultures, LE preparations and a Coombs test were negative. The urine contained a trace to 1+ albumin with from 1 to 15 white cells and occasional red cells. Urine culture grew *A. aerogenes* and enterococci. Glycosuria was never found. Stool examinations for blood, ova and parasites were negative. Prothrombin times, BUN, serum calcium, phosphorus, bilirubin, acid and alkaline phosphatases and cephalin flocculation were normal. Fasting blood sugars were normal but on a glucose tolerance test the blood sugars rose to 190 mg per cent, 200 mg per cent, 209 mg per cent and 179 mg per cent at $\frac{1}{2}$, 1, 2 and 3 hours respectively with no glycosuria. The serum albumin was 2.5 Gm per cent and globulin 3.4 Gm per cent twice and protein electrophoresis also showed low albumin with high alpha 2 globulin. Congo red excretion was 66 per cent of the injected dye. No free acid was present in the fasting stomach but 120 units was present 45 min. after histamine. Thyroidal I^{131} uptake was 34 per cent. Spinal fluid was clear. Pressures, dynamics, cell counts, proteins and cultures were all normal. Blood and spinal fluid serology were negative. Sputum cultures showed *Candida albicans*, coagulase positive hemolytic staphylococcus aureus, beta hemolytic streptococci and *A. aerogenes*. No acid-fast organisms were seen. Liver biopsy specimen was normal. Skin and muscle biopsies showed only muscular atrophy and nonspecific inflammatory and regressive changes in the skin. Bone marrow was hypercellular with some granulocytic hyperplasia.

In the hospital the patient continued to complain of weakness and joint pains. He continued to run a low-grade fever with occasional higher spikes despite various antibiotics. Furthermore, the findings in the chest remained unchanged by auscultation and x-ray. After two months in the hospital, gangrene of the toes of the left foot developed. He was given steroids without apparent effect. The gangrene extended and involved both legs. A large area of necrosis developed on the right leg with no inflammatory reaction. At the end of the third month in the hospital, he became more emaciated, hypotensive and was found dead early one morning.

*Dr. Richard A. Bader**: I was reminded when I read this case history and tried to decide what the patient had, of the quatrain from Omar Khayyam:

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*Myself when young did eagerly frequent
Doctor and Saint, and heard great Argument
About it and about: but evermore
Came out by the same door as in I went.*

Basically, by history, we have a man presumed to have diabetes mellitus, some chronic pulmonary disease characterized by bilateral pulmonary infiltrations, wheezing, hemoptysis and dyspnea. A two-year story of arthritis, some lesions of his leg and some neuropathy or neuromuscular disorder suggest that are dealing here with some diffuse systemic process; whether it is related to the lesion or an independent process remains to be seen.

On physical examination this man was suffering with bronchiolar or bronchial obstruction, emphysematous changes in his chest, and probably peripheral neuropathy. I say probably because of the loss of all modalities of sensation in both motor and sensory components. The fact that there were no abnormal reflex changes would tend to eliminate some long tract disease of the cord. Chest x-ray showed interstitial infiltrations of the lungs which Dr. Wolf will describe.

Dr. Bernard S. Wolf†: A film of the chest was striking. We had actually three examinations of the man during a three week period. The most outstanding features were the densities in both hilar regions, more marked on the left (Fig. 1). Most of these densities were in the hilae as confirmed by oblique and lateral projections. In addition, streaks extended into the periphery of the lung fields. These were not normal pulmonary markings but linear strands of varying thickness. Between the strands lucent areas were seen sometimes ovally shaped in the upper left lobe, and sometimes quite angular in shape. They had the appearance of bullae. Both lungs were emphysematous in a rather generalized fashion. Both domes of the diaphragm were unusually low in position. The transverse diameter of the heart appeared to be somewhat increased and the left ventricular contour of the left margin of the heart was somewhat globular in configuration. The aorta was tortuous. The trachea was displaced somewhat to the right. From a roentgen point of view, this was the so-called bullous emphysema, which in almost all cases is associated with interstitial fibrosis and inflammatory changes. It was not the picture of bronchiectasis. It is seen in late silicosis and occasionally as an end stage in Boeck's sarcoid or late in Christian's disease. In most of the cases that look like this one did, no specific etiology is found and it is labeled as bullous emphysema associated with chronic interstitial inflammatory fibrosis of unknown etiology.

Dr. Bader: We have a chest film which shows bullous emphysema, some increase in fibrous tissue markings of the lung root which could have been an old burned out inflammatory process, as burned out Boeck's sarcoid or burned out silicosis. There is some axis deviation present on the electrocardiogram which suggests the type of pattern one might see due to chronic pulmonary

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hypertension. This type of electrocardiogram indicates possible nonspecific myocardial involvement plus changes secondary to chronic lung disease affecting the pulmonary artery pressure.

The man's chief complaint when he entered the hospital was peripheral neuropathy. I think a good starting point would be to begin there and work from that point of view. The peripheral neuropathy was bilateral and involved all extremities. This suggests a diffuse process. It most likely was toxic or metabolic since it was so symmetrical; for which there are many diseases such as periarteritis nodosa and amyloidosis which can cause isolated neuropathies, I am not talking about pressure neuropathies. It is very unusual for diseases which cause vascular involvement of a specific nerve root to cause such bilaterally uniform neuropathy.

Since this man was diabetic, the first thought that comes to mind was that this was diabetic neuropathy. Diabetic neuropathy can be of several types. The most common type, well recognized by most clinicians, is the diabetic neuropathy involving the lower extremities usually associated with marked pain and sensory involvement and rarely with motor involvement. The picture in our case certainly



FIG. 1. Chest x-ray showing hilar densities.

does not represent the common variety of diabetic neuropathy. Diabetic neuropathy can cause marked motor involvement. When diabetic neuropathy involves all four extremities with marked sensory involvement, it presents a Guillain-Barré type of syndrome. This is called diabetic neuronitis and is characterized very commonly by an elevated spinal fluid protein. Here spinal fluid protein was not elevated and therefore it is less likely that this was diabetic neuronitis. Diabetes mellitus can cause a chronic low-grade peripheral neuropathy with a stocking type of hypesthesia. In favor of diabetic neuropathy we have symmetry, the fact that he was diabetic and the fact that patients with minimal glycosuria may have very severe atherosclerotic and neuropathic disturbances. Further in favor of diabetic neuropathy is the presence of peripheral gangrene in the hospital. In spite of the fact that we were not told what type of pulses the patient had, it certainly suggests that he had diabetic gangrene. Against diabetic neuropathy is the fact that there was motor and sensory involvement without much pain and without elevated spinal fluid protein. The latter also speaks against Guillain-Barré type of syndrome.

It was not likely to be amyotrophic lateral sclerosis because he was old for the disease, his muscle wasting was not associated with fibrillation or fasciculation and hyperflexia with lower motor neuron degeneration was absent. Periarthritis nodosa is known to cause peripheral neuropathy from time to time. However, there are several features about this case which do not fit periarthritis. For example, his blood pressure was normal. His renal findings were minimal. He had no eosinophilia of true allergic background, muscle or abdominal pain, and the symmetrical involvement of all four limbs by neuropathy would be a little unusual in periarthritis nodosa. In favor of periarthritis nodosa are the facts that he has generalized joint pains, hepatosplenomegaly, cutaneous lesions that were necrotic, peripheral gangrene which can occur and usually does terminally, and elevated globulins. However, he did have pulmonary findings. Pulmonary findings in periarthritis are those of eosinophilia pneumonia or episodes of asthma with infiltrations in both lungs such as Löffler's pneumonia. I would be surprised if the lung lesions did show eosinophilic pneumonia. It looks more like bullous emphysema. On x-ray we must consider other diagnoses.

There are diffuse conditions such as amyloidosis that can cause peripheral neuropathy, but this is exceedingly rare. In favor of amyloidosis would be the neuropathy and skin lesions while against it would be the normal Congo red excretion, lack of significant cardiac failure or cardiac symptoms, lack of marked renal findings and albuminuria and the fact that liver biopsy was normal. Finally, several other diagnoses are less likely but should be mentioned for the sake of completeness. While he did not have any adenopathy, he had the lesions on the leg which were irradiated. They could have been the result of some lymphoma and he could have had some lymphomatous process at the base of the lungs because he had a bullous emphysema with some infiltrative or fibrotic process. I do not think it is likely. Another possibility is metastatic bronchogenic carcinoma with peripheral neuropathy. Although he had hemoptysis for ten years, there was no change in the chest x-rays according to the protocol. Von Wegener's

syndrome usually has cartilaginous lesions in the upper respiratory tract and has more marked renal abnormalities. In the absence of cartilaginous lesions and severe renal involvement, I would doubt that the process was Von Wegener's syndrome.

I think it is very unlikely that this was histiocytosis, considering the man's age and the fact that the clinical picture is not explained. This syndrome usually produces a diffuse mottled appearance in the chest x-ray causing an alveolo-capillary block and not obstructive emphysema.

This man had skin lesions described as reddish-brown. Kaposi's sarcoma can cause this type of involvement. Indeed, in the case reported from this hospital, there was invasion of the hilar areas by inflammatory neoplastic tissue. In favor of Kaposi's sarcoma would be the fact that it occurs in males more commonly from 60 to 70 years of age and he did receive radiotherapy which is given for this condition and there are reddish brown plaques which are described and it can cause lung lesions. However, against this is the fact that Kaposi's sarcoma is never necrotic and these lesions were described as necrotic two years earlier. Kaposi's sarcoma is accompanied by edema and the patient did not have edema. Finally, Kaposi's sarcoma rarely causes gangrene.

I think I am left with two basic considerations. If we search for a single diagnosis, we would have to think of periarteritis to explain his neuropathy and arthritis, chronic asthmatic condition from previous years, associated with bullous emphysema, and diabetes mellitus.

If we are thinking of a multiple diagnosis, we have to take diabetic neuropathy with peripheral vascular disease, gangrene, peripheral neuropathy, bullous emphysema, and rheumatoid arthritis. As far as the skin lesions are concerned, we would have to attribute them to diabetic necrosis.

Of the two, while I would like to lean toward periarteritis because it would explain his hyperglobulinemia and joint pain, the involvement of all four extremities forces me away. It is so unusual that I think I have to think of a more diffuse toxic metabolic process such as diabetic neuropathy or one of the unusual neuropathies seen in toxic metabolic disorders such as poisonings or some cryptic malignancy.

*Dr. Mortimer Bader**: I should make the other diagnosis, so one of us will be correct. I will say periarteritis nodosa.

Dr. Alexander B. Gutman†: I think I would agree with one of the Drs. Bader. I do not know quite which one. The story does strongly suggest diabetic neuropathy to me because of the symmetry and the general course of events. The thing that is not explained so far is the very marked weight loss because everything that has been described would hardly account for this course. I think we must be prepared to have some lesion in addition to those already presented and I have been wondering what that would be. I suppose it can be narrowed down to either a generalized infection, of which tuberculosis should be considered very seriously, or a neoplasm tucked away somewhere in the chest that was not

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In Memoriam

SOL WIENER GINSBURG, M.D.

1899-1960

On July 2nd there passed from our midst one of our ablest colleagues and, more significantly, by uniform appraisal of those who knew him, a great human being. Sol Ginsburg died in his sixtieth year after a prolonged illness.

Dr. Ginsburg was born in New York City. Following secondary school and Columbia College he entered the College of Physicians and Surgeons, from which he was graduated in 1924. After serving a medical internship his interest turned first to neurology and then to psychiatry. On completing a residency in neurology at The Mount Sinai Hospital, Doctor Ginsburg pursued graduate studies in both fields in Germany and Holland. He returned to this country and for a period of seven years was a member of the staff in neurology. He left this field in 1937 to devote himself entirely to his chosen career, the study and treatment of mental illness. In both these areas Sol Ginsburg achieved a record of distinguished scholarship, of significant contributions to knowledge and of valuable service in professional and community organizations.

The scope of his diverse interests is revealed by some of the subject matter of his numerous publications. These reveal his concern with "Troubled People," the psychic disturbances resulting from unemployment, the psychiatric aspects of race prejudice, man's attitude toward religious values, and with "Mental Health and the Social Issues of Our Times." Among his more formidable undertakings was his participation in the group studies at Columbia of "The Problem of Occupational Choice," and afterward in the enormous problem of "The Ineffective Soldier." His co-authorship of the three volume monograph detailing the results of the latter study and the widespread acclaim these volumes received from critics, colleagues and the President of the United States, to whom the volumes were dedicated, were, I know, a source of enormous satisfaction to him.

Because of his talent and critical judgment he was sought after in numerous communal enterprises related to the field of psychiatry. Over the years he served on the New York City Committee on Mental Hygiene, the New York City Community Mental Health Board, the Board of Advisors in the Program of Interrelations of Psychiatry and Religion of the Union Theological Seminary, and the National Conference on Mental Health Teaching in Schools of Public Health.

His teaching appointments included service at various periods as Instructor in Psychiatry at The College of Physicians and Surgeons, Associate Professor of Clinical Psychiatry at The Long Island College of Medicine, Lecturer in Psychiatry at The New York School of Social Work, and Clinical Professor of Psychiatry at Albert Einstein Medical College.

Dr. Ginsburg served as Adjunct and Associate Psychiatrist at The Mount Sinai Hospital, Associate Psychiatrist at The Vanderbilt Clinic, Attending



SOL WIENER GINSBURG

1899-1960

Psychiatrist at The Hillside Hospital, and as Attending Psychiatrist to the Veterans Administration.

Recognition of and regard for his qualities of dedication and leadership came to him in his election to the presidency of the Group for the Advancement of Psychiatry (1955-1957) and in 1958, to the presidency of the New York Society for Clinical Psychiatry.

Transcending Sol Ginsburg's distinguished position in his profession was his stature as a human being. He truly combined in himself those noble attributes of the human spirit which are credited to our great religious figures. He had in his character those qualities of perspicacity, understanding, compassion, selfless devotion and integrity which made friends and admirers of all with whom he came in contact. His concern for other people's happiness was never better displayed than in his laborious undertaking of widespread correspondence with his numerous colleagues overseas, and members of The Mount Sinai Unit during World War II, in which, for reasons of health, he was unable to participate. Altruism in its most meaningful sense was here exhibited and lofty purpose served without any of the usual self-consciousness.

The number of patients, friends and colleagues whose lives were touched, re-oriented and bettered by Sol Ginsburg is of course unknown, though it was assuredly great. Added to these whose lives were enriched because of him are the members of his family, and especially his wife Ethel, whose interests and work complemented his own. All these are his mourners. In their consciousness the image of the genial, good humored, lovable, rare human being they had the privilege of knowing, will not fade.

FREDERICK H. KING, M.D.,
for the
Editorial Board

SURGICAL TREATMENT OF CONDUCTIVE DEAFNESS

JOSEPH L. GOLDMAN, M.D.

New York, N. Y.

Since the advent of antibiotics there has existed the erroneous impression not only in the minds of lay people but of physicians as well that otology has become a declining specialty. Nothing could be further from reality than this idea. Actually otology has become one of the most exciting specialties in the field of medicine due to the progress during the past two decades in the restoration of hearing in patients with conductive deafness. The opportunity to restore the sense of hearing in an otherwise healthy individual offers one of the most dramatic rewards in medicine today.

Hearing is dependent on the conveyance of sound from the external ear through the middle ear to the cochlea of the inner ear by a conductive system in which all the structures of the external and middle ears play a part. Once sound is funneled through the external auditory canal to the drum the structures of the middle ear act as a transformer in relaying sound waves to the endolymph of the vestibular labyrinth which, in turn, permits the impulses to reach the end organs of the auditory nerve in the cochlea. Any disturbance in this transformer system will naturally interfere with the conduction of sound (1).

What are these vital structures so necessary for the conduction of sound? In order of activity they are the drum or tympanic membrane, the ossicular chain consisting of the malleus, incus and stapes, the oval and round windows and the eustachean tube. Sound impulses which reach the drum head are transmitted by way of the ossicular chain through the oval window, which contains the footplate of the stapes, to the endolymph of the vestibule. The round window, which is located inferiorly and mesially to the oval window and is an opening in the promontory or inner wall of the middle ear closed off by a membrane, acts to release pressure in the vestibular system which results from the transference of sound waves. The eustachean tube, serving as a conveyor of air between the pharynx and middle ear, helps to maintain the middle ear as an air-containing cavity which is essential for the proper transmission of sound. Thus, sound can fail to reach the cochlear fluid system and finally the end organs of the auditory nerve from any one or a combination of the following causes:

- A) Obstruction of the external auditory canal by cerumen, secretion, atresia or neoplastic growths;
- B) Obstruction of the eustachean tube due to hypertrophied adenoid tissue, infection of the nasopharynx, allergic states or neoplasms;
- C) Infectious secretion or noninfected fluid in the middle ear;
- D) Fixation or interruption of the ossicular chain;
- E) Perforations of the tympanic membrane or chronic infections.

Before delving into the therapeutic considerations of conductive deafness, it

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is pertinent to define conductive deafness audiologically and to indicate how it is determined. In conductive deafness sound is not perceived by viable end organs of the auditory nerve in the cochlea because of failure of transmission along the conductive pathway. Function of the auditory nerve can be determined by degree of bone conduction while amount of hearing can be assessed by conduction of sound by air. Tests can be made crudely with tuning forks and accurately with an audiometer. In conductive deafness the bone conduction perception is better than the air conduction perception (Fig. 1).

OBSTRUCTION OF THE EXTERNAL AUDITORY CANAL

Any substance which occludes the external auditory canal will interfere with the transmission of sound from the external auditory orifice to the drum. The most common obstruction of this type is the collection of large amounts of normal cerumen. The return of hearing after the removal of the cerumen is gratifying. The accumulation of secretion in the external auditory canal from an external otitis, either infectious or eezematoid in origin, can produce the same kind of hearing impairment. Local therapy usually cures the external otitis within a short time.

Obstruction of the external auditory canal also can result from bony atresia or occlusion. This type of obstruction can develop slowly from bony growths such as osteomas which usually are bilateral, or can be due to congenital maldevelopment in which case the external auditory canal has failed to develop. Occluding osteomas can be removed surgically very easily. Treatment of the congenital deformities will depend on the degree of other malformations in the conductive system. Occasionally the obstruction is due entirely to a bony partition which occupies part of the external auditory space. This can be determined by careful roentgenographic study. Removal of the bony partition will restore hearing. When the tympanic membrane or ossicles also are involved in the

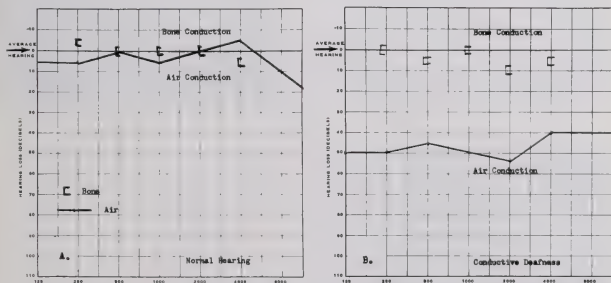


FIG. 1. Audiograms: A, Normal hearing. Note that air conduction and bone conduction are similar. B, Conductive deafness. Note the large air-bone gap as represented by difference in air and bone conduction.

maldevelopment, more extensive operations are required to permit sound to reach the cochlea.

CASE 1

Stenosis of the External Auditory Canal Causing Conductive Deafness

A. E. Age 7. This patient was admitted to The Mount Sinai Hospital because of bilateral hearing loss associated with a malformed right auricle and bony stenosis of the right external auditory canal (Fig. 2A). The left ear was normal (see Case 9 for surgical restoration of hearing of left ear). X-ray examination revealed cellular mastoids. Under general anesthesia a postauricular skin incision was made and the mastoid cortex exposed. The mastoid antrum was opened. The incus was covered by a ledge of bone which was removed and the incudomalleolar and incudostapedial joints were exposed (Fig. 2B). The ossicles were normal and mobile. A full-thickness skin graft was placed over the exposed ossicles (Type II Tympanoplasty-Fig. 2C). An audiogram taken three months after surgery revealed a significant improvement in hearing (Fig. 3).

OBSTRUCTION OF THE EUSTACHEAN TUBE

Patency of the eustachean tube is essential for a normally functioning middle ear. An open and properly functioning eustachean tube assures the middle ear of being filled with air.

In children the most common cause of obstruction of the eustachean tube is the presence of hypertrophied and infected adenoid tissue. Adenoid tissue can produce conductive hearing losses of 20 to 30 decibels. The treatment is removal of the adenoid tissue and the method deserves special mention. Although tonsillectomy is usually a standardized procedure, the same cannot be said for adenoidectomy. The thorough removal of adenoid tissue, particularly about the

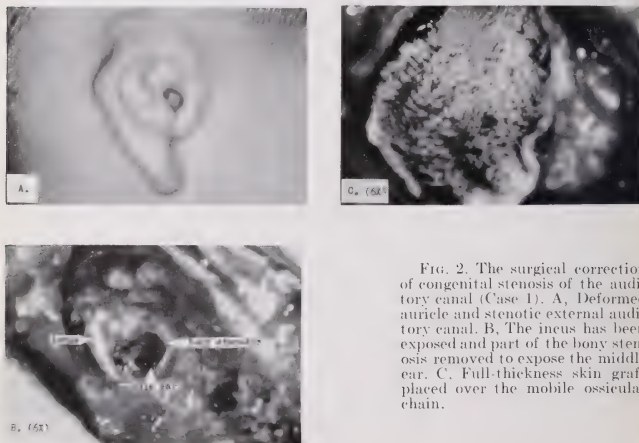
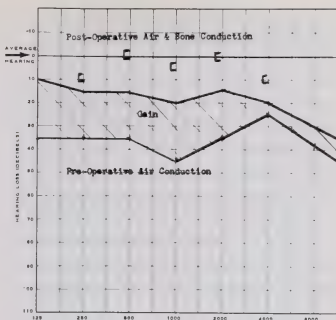


FIG. 2. The surgical correction of congenital stenosis of the auditory canal (Case 1). A, Deformed auricle and stenotic external auditory canal. B, The incus has been exposed and part of the bony stenosis removed to expose the middle ear. C, Full-thickness skin graft placed over the mobile ossicular chain.

FIG. 3. Audiogram showing 20 db hearing improvement one month after surgical correction of congenital stenosis of the auditory canal (Case 1).



eustachean orifice, is not a simple procedure. This operation is not always performed with the necessary meticulous care. Complete adenoidectomy requires direct visualization of the nasopharynx, including the regions of the eustachean tube orifices, and the implementation of special instruments such as small curettes and punch forceps.

Not infrequently conductive deafness occurs in a child who has had a previous adenoidectomy. Such a situation requires further evaluation of the nasopharynx for residual or reformed adenoid tissue. In my opinion the only diagnostic methods with which one can accurately appraise the status of adenoid tissue are either direct mirror visualization of the nasopharynx, which cannot be accomplished with many children, or lateral soft tissue roentgenography of the nasopharynx (2). Whenever tissue masses are visible or discernible, surgery should be the treatment of choice. I believe that x-ray or radium therapy should be utilized only if all other treatment has failed.

CASE 2

Postoperative Adenoidal Enlargement, Ear Infection, Impaired Hearing

C. F. Age 7. A tonsillectomy and adenoidectomy had been performed on this patient at the age of two. For the following five year period he had repeated infections of the ears and upper respiratory tract. His hearing became impaired. A second adenoidectomy was performed eight months prior to his first visit, but hearing did not improve. Examination revealed no evidence of nasal or sinus disease. The tympanic membranes were congested and retracted. An audiogram indicated a moderate conductive hearing loss. Lateral soft tissue roentgenograms of the nasopharynx showed enlarged adenoids high in the vault (Fig. 4A, B). Following this operation the tympanic membranes assumed a normal appearance and the hearing returned to normal (Fig. 5).

Often a secretory otitis media is associated with obstruction of the eustachean tube by infected adenoids. This subject will be discussed later, but at this point it should be mentioned that myringotomy with aspiration of the secretion should be performed at the time of the adenoidectomy if fluid is suspected to exist in the middle ear.

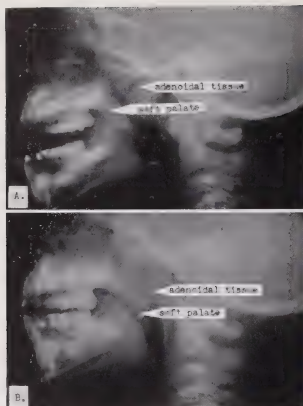


FIG. 4. Lateral soft tissue roentgenograms showing narrowing of the nasopharyngeal space by adenoidal tissue (Case 2). A, Enlarged adenoids during inspiration. B, Enlarged adenoids with respiration suspended prior to third operation. Note complete occlusion of nasopharyngeal airway.

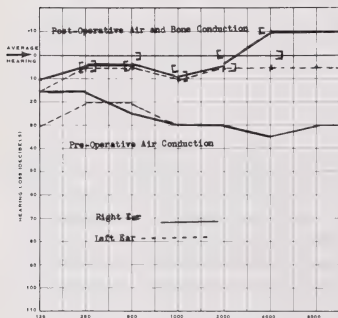


FIG. 5. Audiogram showing bilateral hearing improvement after thorough adenoidectomy (Case 2).

Infection of the nasopharynx and allergic states can affect the eustachian tube and thus produce impaired hearing in adults as well as in children. Obstruction of the eustachian tube can result from intrinsic inflammatory or allergic edema with thickening of the tissues of the eustachian tube. These tissue reactions most often are transient but may become permanent if the irritating sources are not removed. Ultimately it may become necessary to dilate the eustachian tube by bouginage. It is desirable, of course, to treat the nasopharyngeal and eustachian problem during the early phase of infection and allergy (3).

The type of nasopharyngeal infection which influences eustachian tubes invariably is associated with nasal and sinus infections. When the edema in the eustachian tube is noninfectious in origin, vasomotor rhinitis is usually the

cause. The term vasomotor rhinitis is used in the broad sense to include specific allergic reactions, physical allergy and constitutional reactions including those of psychosomatic origin.

Thus, to evaluate this problem, a thorough investigation of the nasal and sinus status is necessary. This includes x-ray of the sinuses as well as the nasopharynx, diagnostic irrigation of the maxillary antrums and sometimes the other sinuses, and bacteriologic and cytologic studies of secretion from the nose and sinuses. The bacteriologic and cytologic investigation is essential to differentiate accurately between an infectious and an allergic process. This distinction cannot be revealed grossly by the amount or kind of secretion obtained.

Finally, therapy should be directed either to cure the nasal or sinus infection and thus the nasopharyngeal infection, or to control the allergic reactions. This involves irrigation of the sinuses, the use of appropriate antibiotics as indicated by sensitivity tests, hyposensitization to positive allergens and other measures to control vasomotor reactions.

It is especially important to detect nasopharyngeal carcinomas early since some of these tumors, such as the transitional cell and the embryonal cell carcinomas, may be sensitive to radiation. One of the earliest symptoms of nasopharyngeal carcinoma or other less common neoplasms may be conductive deafness in one ear due to obstruction of the eustachean tube orifice. This emphasizes the need for thorough nasopharyngeal examination in all patients with conductive deafness.

CASE 3

Nasopharyngeal Tumor Causing Unilateral Conductive Deafness

E. C. Age 55. This patient was seen in 1957 with the chief complaint of unilateral hearing loss of three months duration. Initial examination revealed a unilateral right-sided conductive deafness with normal external auditory canals. The tympanic membranes were noted to be slightly retracted. The nasopharyngeal examination revealed a small granular mass about the orifice of the right eustachean tube. No cervical lymphadenopathy was noted. A nasopharyngeal biopsy specimen was taken and revealed fragments of embryonal cell carcinoma (Schminke tumor). The patient was given Cobalt-60 teletherapy, 6000 R, through two portals. The tumor disappeared and at the present time, three years later, the patient is asymptomatic and free from disease. A current audiogram shows complete restoration of hearing (Fig. 6).

INFECTIOUS AND SECRETORY OTITIS MEDIA

Collection of secretion of fluid in the middle ear space interferes with the transference of sound by its influence on the ossicles and the movement of the membrane of the round window, thereby creating conductive deafness (4, 5).

The impaired hearing associated with acute infections of the middle ear usually is temporary. At present there is a tendency to treat such infections solely with antibiotic drugs. In other words, the reliance is on the absorption of the purulent secretion and drainage through the eustachean tube. Contrary to this attitude many otologists believe that middle ear infections which produce high fever and great pressure on the drum and consequently considerable pain should be drained by myringotomy. Those performing middle ear surgery are now seeing instances of conductive deafness caused by adhesions surrounding the ossicles.

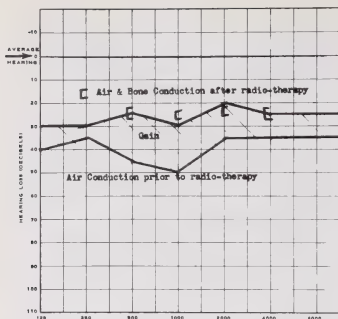


FIG. 6. Audiogram showing hearing improvement after course of Cobalt-60 teletherapy in the treatment of Schminke tumor of the nasopharynx (Case 3).

These adhesions must have resulted from previous infections or even possibly from the collection of noninfected fluid. Draining severe infections of the middle ear by the performance of a myringotomy may in some patients prevent consequent loss of hearing.

From the point of view of conservation of hearing I believe that the condition of secretory or serous otitis media is more important. The presence of fluid in the middle ear as a cause of conductive deafness exists much more frequently than is commonly thought. Its occurrence is usually insidious and associated with obstruction of the eustachean tube, although it may exist without such obstruction being obviously manifest. On examination, presence of fluid may be indicated by the appearance of a fluid level or brownish or bluish discoloration behind the drum. Frequently, however, there may be no alterations of the tympanic membrane to suggest the existence of fluid in the middle ear.

Aspiration of the middle ear quite often yields fluid when there is audiologic evidence of conductive deafness and no other obvious cause of the deafness can be ascertained. Once the presence of a secretory or serous otitis media is established, therapy should be directed to eliminate the cause and to rid the middle ear of the fluid. Etiologic factors may be infection of the nose and sinuses, hypertrophied and infected adenoid tissue, allergic reactions of the upper respiratory tract, and a poorly functioning eustachean tube. The fluid may be clear, amber and watery in character, or thick, viscid and whitish or grayish. At all times this type of fluid or mucoid secretion is free from infection. Active treatment of the middle ear involves either repeated aspirations, myringotomy in instances of thick, viscid secretion or unsuccessful repeated aspirations, or the insertion of a thin polyethylene tube into the middle ear to permit constant drainage.

CASE 4

Middle Ear Effusions Causing Conductive Hearing Loss Treated With Bilateral Myringotomy

S. M. Age 3. This patient was first seen in December 1958 because of repeated sore throats, ear infections and obstructed breathing. A tonsillectomy and adenoidectomy were per-

formed. The patient was well until June 1959 when examination revealed retracted ear drums with an orange color hue behind the drums. An audiogram showed a moderately severe bilateral conductive hearing loss. Myringotomies were performed and thick mucoid secretion was aspirated from both middle ears. An audiogram taken three weeks after the myringotomies showed an improvement in hearing (Fig. 7).

An acute instance of serous otitis media is seen after rapid airplane descents, usually in the presence of an upper respiratory infection. This type of middle ear reaction is called *aero-otitis* and evidence of hemorrhage in the middle ear or tympanic membrane or blebs on the membrane may be present. Release of fluid from the middle ear or from the blebs by aspiration, myringotomy or puncture may yield considerable relief of pain and hasten recovery (6).

FIXATION OR INTERRUPTION OF THE OSSICULAR CHAIN

The ossicular chain constitutes one of the most important links in the conduction of sound in the ear. It has been estimated that the three ossicles, the malleus, incus and stapes, contribute about 25 decibels to the conductive hearing mechanism. In other words, elimination of ossicular conduction of sound by fixation or interruption of the ossicular chain theoretically should reduce hearing by at least 25 decibels.

The most frequent form of ossicular fixation, or stapes fixation to be precise, is represented by the condition known as *otosclerosis*. Otosclerosis, in turn, is the most frequent cause of chronic progressive deafness in adults. The pathologic condition consists of the replacement of normal bone by a new kind of vascular bone. When this bone impinges on or invades the footplate of the stapes in the oval window, various degrees of ankylosis occur. One of eight individuals with evidence of histological otosclerosis exhibits clinical otosclerosis or conductive deafness. Studies of this disease strongly suggest an hereditary tendency (7).

As this disease progresses, a perceptive deafness becomes superimposed on the conductive deafness. The perceptive component of the deafness, of course, cannot be altered once it occurs. However, it is significant that a successful opera-

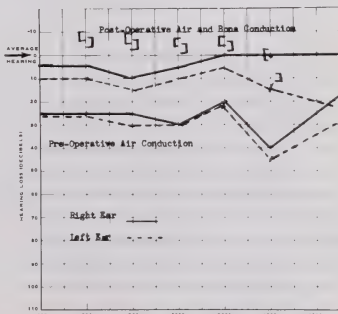


FIG. 7. Audiogram showing bilateral hearing improvement after myringotomies in the treatment of secretory otitis media (Case 4)

tion for the conductive deafness often stops or inhibits the progression of the perceptive element of the disease.

The rehabilitation of hearing in patients with otosclerosis provides one of the outstanding chapters in the history of medicine. The two operative procedures which have been responsible for this great contribution to humanity are the fenestration of the osseous horizontal semicircular canal introduced by Lempert in 1938 (8) and mobilization of the stapes initiated by Rosen in 1953 (9).

It is of interest that the earliest attempt to cure deafness from otosclerosis operatively was directed to the stapes itself. Such efforts began in 1878 when Kessel of Germany tried to mobilize the stapes through the posterior part of the tympanic membrane (10). The largest series and most explicit account of that period was reported in 1890 by the French otologist Miot (11). His statistics were based on 200 stapes mobilization operations with many favorable results; his method and observations were similar in a number of respects to the operation recently introduced by Rosen. In 1892 and 1893 Blake (12) and Jack (13) in this country attempted to improve hearing by removing the stapes.

For reasons that have not been clearly disclosed in the literature, the stapes mobilization operation was abandoned towards the end of the last century. The only relative positive statement was made by Siebenmann of Switzerland who wrote, "Clinical experience teaches that all endeavors at mobilization of the stapes in otosclerosis are not only useless but often harmful (14)".

Thus, it was not until 1953 when Rosen described his operation of stapes mobilization that this procedure once more became prominent for the treatment of deafness due to otosclerosis.

The greater success of the present stapes mobilization operation has been influenced undoubtedly by the availability of magnification offered by loupes and the operating microscope, superior illumination, antibiotics, and improvement and better training in operative techniques.

The other significant approach in the surgical treatment of otosclerosis has been to by-pass the otosclerotic lesion of the oval window, and to make an opening in the bony labyrinth or semicircular canal. During the second and third decades of this century Holmgren of Sweden, who is regarded as the father of the fenestration operation, contributed immensely to the progress of fenestration of the horizontal semicircular canal for the treatment of otosclerotic deafness (15). It remained for Lempert to bring this work to a brilliant conclusion when he presented his one-stage endaural fenestration operation of the horizontal semicircular canal in 1938.

Until approximately seven years ago, fenestration of the horizontal semicircular canal was the only surgical procedure available for the treatment of otosclerotic deafness. Fenestration, in a sense, is a type of modified radical mastoidectomy and a permanent mastoid cavity results. This requires permanent care and avoidance of contact with water. The postoperative course usually is more involved than after stapes surgery.

In mobilization of the stapes the ossicles are exposed by elevating the drum through the external auditory canal. It is often necessary to remove some bone

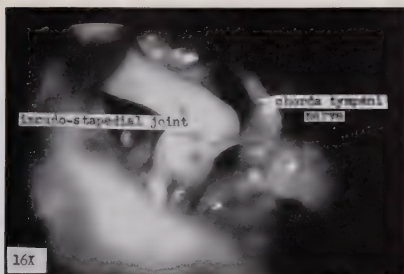


FIG. 8. Initial exposure of the incudostapedial joint and chorda tympani nerve during stapes surgery.

of the posterior canal wall overlying the ossicles. Care must be taken to spare the chorda tympani nerve (Fig. 8). Mobilization of the stapes can be accomplished by manipulations directed to the neck, head or footplate of the stapes.

CASE 5

Otosclerosis Treated by Bilateral Stapes Mobilization

M. S. Age 45. This patient was first seen at The Mount Sinai Hospital in 1957 with hearing loss and tinnitus of eight years duration. There was no history of vertigo. The patient's sister was known to have a conductive hearing loss. Physical examination revealed no abnormalities. An audiogram showed bilateral conductive deafness. In November 1957 a right stapes mobilization was performed. Mobilization was obtained by pressure at the head of the stapes. In November 1958 a left stapes mobilization was performed by pressure at the head and footplate of the stapes. An audiogram taken in November 1959 showed that the initial hearing improvement has been maintained (Fig. 9).

The percentage of successful results is better with the fenestration operation than with the mobilization operation. Although the percentages vary with different surgeons, approximately 60 to 70 per cent of the patients have improved hearing after the fenestration operation and 40 to 50 per cent after the stapes mobilization operation (16-18).

One cannot, however, accurately compare the stapes mobilization and the fenestration procedures by looking solely at the percentage of successful results. The stapes mobilization operation has a greater field of application, that is, it may be employed whenever there is any significant conductive component in a patient's deafness. The fenestration operation should be performed only when there is good cochlear reserve as evidenced by good bone conduction. In the fenestration operation, since the ossicular chain is by-passed, a successful result usually will leave a hearing deficit of about 25 decibels below the cochlear reserve. For example, a patient who has a conductive hearing loss of 25 decibels theoretically has little to gain from the fenestration operation, whereas this loss may be completely eliminated with mobilization of the stapes. Therefore, most

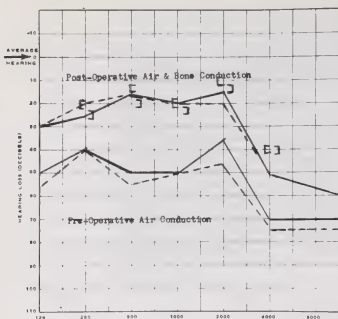


FIG. 9. Audiogram showing bilateral hearing improvement after successful stapes mobilizations in the treatment of otosclerosis. The right audiogram is two years post-operative and the left one year postoperative (Case 5).

otologists believe that stapes mobilization is the procedure of first choice for the patient with clinical otosclerosis.

There are certain inherent disadvantages in the mobilization procedure. Many fixed stapes cannot be mobilized and others once mobilized may later become refixed; this accounts for the lower long term results than with the fenestration operation. It should be emphasized, however, that if an initial attempt to mobilize the stapes should fail, a second operation on the stapes or a fenestration operation can be performed.

CASE 6

Otosclerosis Treated by Fenestration of the Horizontal Semicircular Canal

B. V. Age 37. This patient was seen in 1957 because of progressive hearing loss since the age of twelve. Hearing had decreased following each of the patient's five pregnancies. Physical examination revealed normal auditory canals and tympanic membranes. An audiogram showed bilateral conductive hearing loss. The patient was admitted to the hospital for a stapes mobilization under local anesthesia. The drum was elevated and it was noted that the stapes was completely fixed; no mobility could be obtained. She was discharged on the second postoperative day and readmitted three months later for a fenestration nov-ovalis (Lempert) procedure. This was performed under general anesthesia. A fenestra was created in the horizontal semicircular canal and covered with a tympanomeatal flap. The postoperative course was uneventful. An audiogram taken one year after surgery shows that the initial hearing improvement has been maintained (Fig. 10).

Recently Shea and others concerned with the long-term results obtained with stapes mobilizations have suggested a new approach to this problem (19). The rigidly fixed stapes is removed from the oval window and a new sound-conducting mechanism constructed. A small autogenous vein graft is placed over the patent oval window and a 3 to 4 mm piece of No. 90 polyethylene tubing, the prosthesis, is placed between the graft and the lenticular process of the incus. The immediate improvement in hearing noted and the high percentage of good results are remarkable (20). However, many questions regarding this procedure remain

unanswered, such as, the effect of this operation on the inner ear and the eventual fate of the polyethylene tube.

Very recently, Kos (21) and Schucknecht (22) have reported a new type of prosthesis, namely the use of vein and fat plugs which fill the oval window and which are held in place by tantalum or steel wire attached to the long process of the incus.

CASE 7

Otosclerosis Treated by Fenestration of the Oval Window with the Insertion of a Vein Graft and Polyethylene Prosthesis

M. L. H. Age 24. This patient was first seen in 1953 at the age of 17 with the complaint of tinnitus and hearing loss. Physical examination revealed normal auditory canals and tympanic membranes. An audiogram showed an average 30 db hearing loss in the right ear and a 40 db hearing loss in the left ear. A hearing aid was prescribed. In 1957 and 1958 stapes mobilizations were performed with a temporary restoration of hearing. By the fall of 1959 hearing had decreased further and in December 1959 the right ear was re-explored. The stapes was found to be firmly ankylosed again (Fig. 11A). The head and crura of the stapes were removed (Fig. 11B). The stapedial footplate had been replaced with dense, white otosclerotic bone (Fig. 11C). This was removed with microsurgical diamond drills and the open oval window was covered with an autogenous vein graft (Fig. 11D, E). A 3.5 mm polyethylene prosthesis was inserted between the lenticular process of the incus and the vein graft (Fig. 11F). The patient noted a considerable hearing improvement which has been maintained for six months (Fig. 12).

Some surgeons have placed the prosthesis between the incus and footplate (after removal of head and crura) when the latter can be mobilized and thereby have eliminated the need of a vein graft.

CASE 8

Otosclerosis Treated by Mobilization of Stapedial Footplate with Insertion of Polyethylene Prosthesis

R. R. Age 54. This patient was admitted to The Mount Sinai Hospital because of bilateral conductive deafness of 25 years duration. She wore a hearing aid for more than ten years.

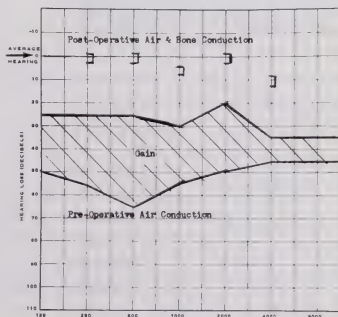


FIG. 10. Audiogram showing 30 db hearing improvement one year after fenestration of the horizontal semicircular canal in the treatment of otosclerosis (Case 6).

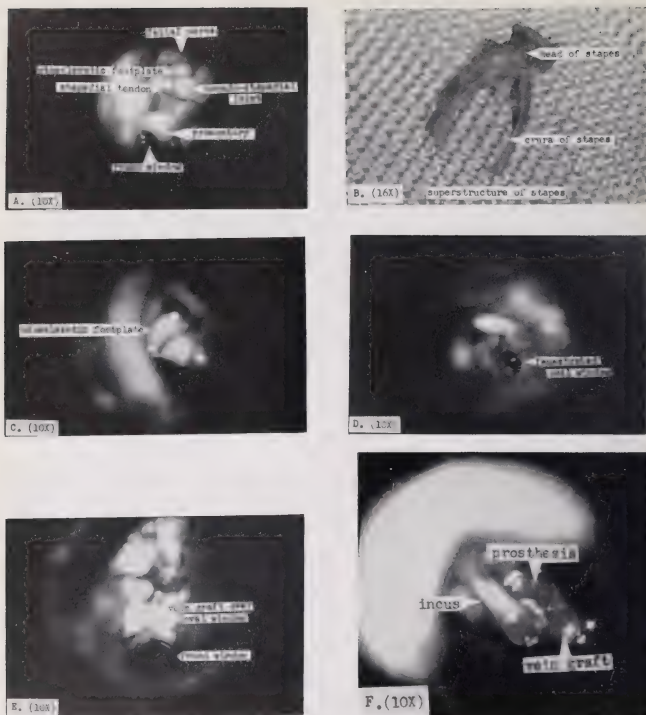


FIG. 11. Fenestration of the oval window with the insertion of a vein graft and polyethylene prosthesis in the treatment of otosclerosis. A, Operative exposure showing otosclerotic footplate, incudostapedial joint, facial nerve, stapedial tendon, promontory and round window. B, Superstructure removed consisting of head and crura of the stapes. C, Dense, white otosclerotic footplate. D, Fenestrated oval window. E, Vein graft placed over open oval window. F, Polyethylene prosthesis between incus and vein graft.

A sister and brother were known to have impaired hearing. Examination revealed normal external auditory canals and tympanic membranes. An audiogram showed marked conductive hearing loss in both ears. There was no history of tinnitus or vertigo. A diagnosis of otosclerosis was made. In February 1960 a right middle ear exploration was done. The stapes was found to be fixed and in attempting to mobilize it both crura were fractured. The superstructure was removed and the footplate was noted to be firmly fixed. Working with sharp picks at the margin of the footplate, complete mobility was obtained and a small linear fenestra was created along the promontory side of the stapes footplate. This was covered with gelfoam and a 3.5 mm polyethylene prosthesis was inserted between the

FIG. 12. Audiogram showing 30 db hearing improvement six months after fenestration of the oval window with the insertion of a vein graft and polyethylene prosthesis in the treatment of otosclerosis (Case 7). Note that there is no residual air-bone gap.

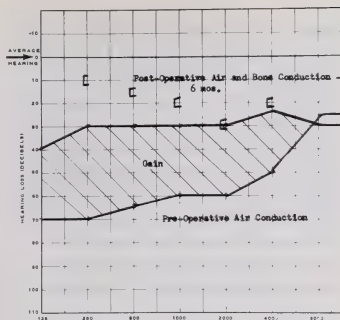
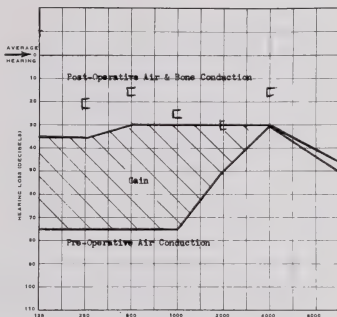


FIG. 13. Audiogram showing 40 db hearing improvement four months after insertion of a polyethylene prosthesis on a mobile stapes footplate in the treatment of otosclerosis (Case 8).



incus and the mobile footplate. An audiogram taken four months postoperatively revealed a marked gain in hearing (Fig. 13).

Other conditions causing fixation of the ossicles are encountered much less frequently than otosclerosis. Adhesions and fibrous processes surrounding or enmeshing the ossicles as a consequence of previous infection or secretory disease of the middle ear can be responsible for fixation of the ossicles. The malleus and incus as well as the stapes may be involved in this type of hearing impairment. An attempt should be made to separate the fibrous tissue which limits the mobility of the ossicles and to prevent refixation of the scar tissue. The middle ear is exposed through the external auditory canal as in the stapes mobilization operation.

The ossicles also can be fixed in various ways in congenital malformations of the middle ear. This entity is characterized by marked conductive hearing loss

with onset noted early in life. The exact procedure performed for its correction will depend on findings disclosed at the time of operation. For example, if the malleus and incus are found to be deformed and fixed, it may be necessary to remove them and to reconstruct a sound-conducting mechanism as will be described later in the section on tympanoplastic procedures. A variety of problems may be revealed which will test the imagination and skill of the otologic surgeon (23).

Actual interruption of the ossicular chain, particularly between the incus and stapes, also can occur, although infrequently. The incudostapedial joint can be separated by accidental dislocation of the incus in mastoid operations. This separation can happen rarely in severe jolting injuries to the side of the head. In these cases there is conductive deafness with very good nerve function. When the middle ear is exposed, the incudostapedial joint is found completely separated. Efforts should be made to reunite the joint. If this fails, the other procedures described to create a continuous conductive mechanism should be attempted (25).

CASE 9

Congenital Malformation in the Middle Ear Causing Conductive Deafness

A. E. Age 7. This patient was seen at The Mount Sinai Hospital because of hearing loss since birth. Examination revealed a normal left auricle, external auditory canal and tympanic membrane. The right ear had previously been operated on for congenital bony stenosis of the auditory canal (Case 1). Because of the known congenital anomaly of the right ear, it was believed that this patient had a congenital malformation in the left ear causing deafness. The left middle ear was explored in May 1960 under general anesthesia. After the tympanic membrane was elevated it was noted that the end of the long process of the incus consisted of a fibrous band attached to the stapes. The stapes itself was malformed and fixed. The stapedial mass was mobilized with fine picks and a small piece of bone removed from the external auditory canal wall was wedged between the malformed incus and stapes (Fig. 14). A slight movement of the malleus was then seen to be transmitted through the newly created ossicular chain to the oval window. An audiogram taken one month after surgery revealed a 25 db hearing improvement (Fig. 15).

PLASTIC CONSTRUCTION OF THE MIDDLE EAR

Further significant strides were made in the surgical therapy for conductive deafness when Zollner in 1951 (26) and Wullstein in 1952 (27), both of Germany, applied methods of plastic and reconstructive surgery in the treatment of perforations of the tympanic membrane and chronic infections of the middle ear and mastoid.

The feasibility of this approach has been aided by the availability of antibiotics, magnification as provided by the operating microscope, an increased knowledge of the techniques of preparing and handling of skin grafts, and a better understanding of the physiologic mechanisms of hearing (28).

In these surgical reconstructions of the middle ear, an attempt is made to recreate an air-containing middle ear space which will transmit sound energy to the oval window utilizing the intact components of the ossicular chain. Essential prerequisites for this type of surgery are good bone conduction levels and a patent eustachean tube.

FIG. 14. Reconstruction of the ossicular chain in a patient with congenital anomaly of the middle ear by placing a small bone graft wedge between the malformed incus and stapes (Case 9).

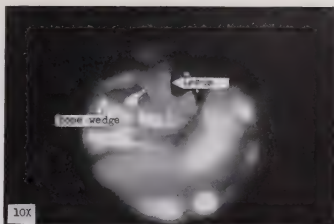
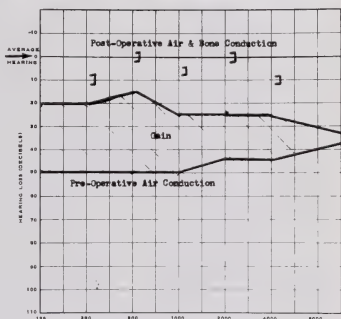


FIG. 15. Audiogram showing immediate hearing improvement after reconstructing a mobile ossicular chain in the treatment of incudostapedial joint deformity as a cause of conductive deafness (Case 9).



Plastic reconstruction of a perforated tympanic membrane is known as myringoplasty. As a rule, a perforated tympanic membrane is associated with an intact ossicular chain and will yield an air conduction perception loss not more than 30 decibels. The suitability of such cases for plastic reconstruction can be determined by a patch test, which consists of covering the opening of the tympanic membrane with a substance such as cigarette paper. A favorable test will show improved hearing immediately. There should be absolute control of supuration before myringoplasty is attempted. This may involve the clearing of adenoidal, sinus and pertinent allergic problems.

The term tympanoplasty is now used to describe surgical reconstructions of the middle ear conductive hearing mechanism that has been altered by infection. The surgical concepts of tympanoplasty are attempted at present in the treatment of chronic middle ear and mastoid disease when there is evidence of a conductive hearing impairment with a sufficient air-bone gap and thus cochlear reserve to anticipate a useful hearing result. This involves the preservation of all healthy tissue in the middle ear, particularly the ossicles, which are required in the operation to improve hearing while all the diseased tissues are removed with the help of the operating microscope. The precise contact of the skin graft which

forms the new tympanic membrane with the available ossicles, determines the type of tympanoplasty created and the possible predictable hearing result.

As in the case of otosclerosis, serviceable hearing may be expected from these operations when the average bone conduction loss in the speech frequencies is not more than 25 to 30 decibels. However, desirable improvement can be obtained when the bone conduction loss is greater than this figure. The air conduction perception provides useful information in interpreting the integrity of the ossicular chain. Usually an air conduction perception with a loss of 40 to 50 decibels points to a reparable ossicular chain by a reconstructive procedure while a greater loss than this reading usually indicates irreversible damage to the ossicular chain. In these latter instances, however, a functioning stapes alone can be utilized in reconstructive surgery, or it may be necessary to resort to fenestration of the horizontal semicircular canal or to the use of a prosthesis in the attempt to restore hearing.

In all these procedures a postauricular full-thickness skin graft has been found to be especially suitable. The placing of the graft and the preparation of its bed depend on the functioning structures found at the time of operation. The operation is best performed by entering the external auditory canal postauricularly. Its successful completion often taxes the ingenuity of the surgeon.

CASE 10

Traumatic Perforation of the Ear Drum with Hearing Loss

L. W. Age 6. This patient was referred to The Mount Sinai Hospital in November 1959 because of unilateral hearing loss. Two weeks before admission she had placed a bead in the right external auditory canal and had been taken to another hospital to have it removed. During removal of the bead she experienced severe pain, bleeding and a significant loss of hearing. Examination revealed that only a rim of tympanic membrane was intact. The handle of the malleus, the incudostapedial joint, the promontory and round window niche could be seen through a large central perforation. There was no evidence of infection. An audiogram revealed a 50 db conductive hearing loss in the right ear. Surgical treatment was deferred until spring in order to allow any spontaneous regeneration to occur. During

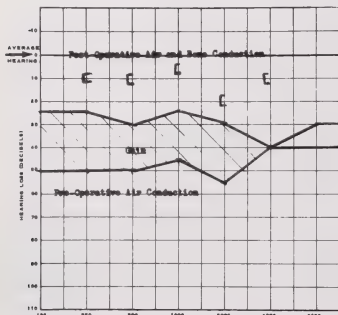


FIG. 16. Audiogram showing hearing improvement one month after closure of a perforated tympanic membrane by a full-thickness skin graft (Case 10).

this interval she had her tonsils and adenoids removed. In May 1960 the patient was readmitted to this hospital and under general anesthesia a postauricular skin incision was made and a segment of full-thickness skin was removed. The drum remnant was denuded of its epithelium and a bed was prepared for the required skin graft. This was placed in position and held with small pieces of gelfoam and cotton pellets (Tympanoplasty Type I). An audiogram taken one month postoperatively showed a 25 db hearing improvement (Fig. 16). Clinical examination revealed complete closure of the previously described perforation.

SUMMARY

It is one of the great achievements in medicine to restore a sense to a serviceable degree. The surgical procedures now available in otology offer such an opportunity so that today many patients with conductive deafness may expect to regain their hearing.

Conductive deafness can be helped by various procedures. In some instances the problem is a simple one, in others intricate techniques requiring skill and considerable understanding are involved. The fact is that help can be offered to patients with conductive deafness due to different conditions, such as, obstruction of the external auditory canal and eustachean tube, collection of fluid and secretion in the middle ear, fixation or interruption of the ossicles, perforations of the tympanic membrane and chronic middle ear disease. The progress that has been made during the past two decades in the restoration of hearing in conductive deafness, particularly in otosclerosis and in chronic middle ear disease, represents one of the illustrious developments in medicine of this era.

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NON-DISJUNCTION OF THE CHROMOSOMES AS A CAUSE OF CONGENITAL DEFECTS: KNOWN AND POTENTIAL COMBINATIONS

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Improved methods of counting chromosomes, utilizing tissue cultures, have established that the normal human nucleus contains a total of 46 chromosomes, instead of 48 chromosomes which was previously believed (1-8). The technique involves the introduction of colchicine into the medium to arrest cellular division at spindle formation, followed by the addition of hypotonic saline to separate the chromosomes. The cells are then fixed, squashed and stained. A photomicrograph of the nucleus is enlarged and the chromosomes are cut out, measured and paired according to their morphology. Twenty-two paired somatic chromosomes (autosomes) and a pair of sex chromosomes designated as xx in the normal female and xy in the normal male have been identified. The y chromosome is approximately one-third the size of an x chromosome (5).

The primary spermatocyte and primary oocyte (Fig. 1) undergo two maturation divisions in order to produce the haploid number of 23 chromosomes found in the mature sperm or ovum (9, 10). Each of the original 46 chromosomes contains a centromere (deeply staining body) which acts differently in the two maturation divisions. The first maturation division (meiosis) is reductional, *i.e.* each member of a pair of homologous chromosomes separates so that 23 chromosomes, each with a centromere, are found in the secondary spermatocyte or oocyte. Each chromosome, which has already split into two strands (chromatids) is held together by the centromere at this stage. The second maturation division involves the splitting of the centromere, with the spermatid or ootid receiving one chromatid from the pair that was held together by the centromere (total complement—23 chromatids and 23 centromere halves).

In the abnormal process of non-disjunction, a pair of homologous chromosomes do not separate so that at division the nonseparated chromosomes are in one cell, leaving the other cell devoid of a chromosome (11). In the human, the x and y chromosomes are frequently unpaired in the primary spermatocyte during spindle formation (2). Both chromosomes could migrate to the same pole resulting in a sperm that possesses both an x and y chromosome, or one that contains no sex chromosome. Non-disjunction of the x chromosome in the primary oocyte could produce either an ovum with an xx combination or no sex chromosome (4) (Fig. 1).

The recent observations of abnormal sex chromosome combinations (xo, xxx, xxy) in certain congenital gonadal defects suggest that non-disjunction of the sex chromosomes is most common during the first maturation division. (In order

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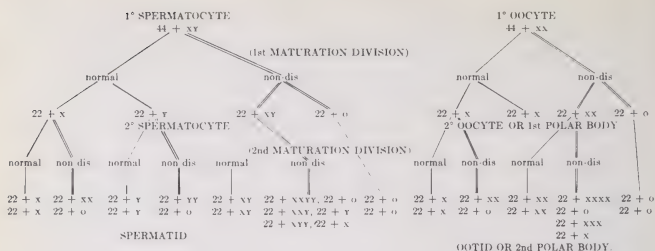


FIG. 1. Maturation division and non-disjunction

to clarify which parent is donating the x, the maternal donation shall be designated as x', xx' or o' for the remainder of the paper.)

XO—45 CHROMOSOMES—TURNER'S SYNDROME

The eponym of Turner's syndrome (Bonnevie-Ulrich-Turner Syndrome) (12, 13) refers to the association of certain congenital anomalies, dwarfism and gonadal aplasia (absence of all germ cells with lack of development of the gonads, so that a vestigial streak is seen in the broad ligaments) (14). The observations of abnormal chromosome counts containing only a single x chromosome (xo) suggest the genetic origin of this syndrome with non-disjunction as the cause (4, 7, 15-19). A patient with an xo Turner's syndrome could be produced by the union of a normal /x/ ovum with an o sperm or an /o/ ovum with an x sperm (x o or 'o x) (Table I). There is suggestive evidence that non-disjunction during spermatogenesis is more frequently the cause of the xo Turner's syndrome, (4, 20, 21) although occasionally oogenesis may be at fault (19).

The female appearance (phenotype) of the patient with Turner's syndrome (xo) having only half of the normal quantity of female-determining genes requires explanation. In the usual course of fertilization, if the sperm and the ovum contain a normal x sex chromosome, ovaries develop from the fetal gonadal cortex. If a sperm containing a normal y sex chromosome fertilizes a normal x containing ovum, testes develop from the fetal gonadal medulla (10). The developing medulla of the fetal testis is believed to secrete an androgenic substance which causes Wolffian duct development (epididymis, vas deferens and seminal vesicles) with regression of Müllerian duct elements (the primordia of fallopian tubes, uterus and vagina) (11, 22). Jost established the relationship of this "androgenic hormone" to the physical appearance of the fetus (23). If rabbit embryos have their immature gonads removed before a crucial stage of genital duct differentiation, all will develop into sterile (agonadal) individuals having the outward anatomic appearance (phenotype) of a female and female internal sex ducts. The human counterpart is the Turner's syndrome patient with infantile female external genitalia, vagina, uterus and tubes, in accordance with

TABLE I
Possible Sex Chromosome Combinations in Zygote Produced by Non-disjunction During Spermatogenesis and Oogenesis

	Normal Sperm		1st Maturation Division Non-disjunctive Sperm		2nd Maturation Division Non-disjunctive Sperm				
	X	Y	XY	O	XX	O	YY	XXYY	XXY
Normal Ovum	/X/X	/Y/Y	/X/XY	/X/O	/X/XX	/X/O	/X/XY	/X/XXYY	/X/XXY
1st Mat. Div. Non-dis Ovum	/XX/X /O/X	/XX/Y /O/Y	/XX/XY /O/XY	/XX/O /O/O	/XX/XX /O/XX	/XX/O /O/O	/XX/XY /O/XY	/XX/XXYY /O/XXYY	/XX/XXY /O/XXY
2nd Mat. Div. Non-dis Ovum	/XX/X /XXXX/X /O/X /XXX/X	/XX/Y /XXXX/Y /O/Y /XXX/Y	/XX/XY /XXXX/XY /O/XY /XXX/XY	/XX/O /XXXX/O /O/O /XXX/O	/XX/XX /XXXX/XX /O/XX /XXX/XX	/XX/O /XXXX/O /O/O /XXX/O	/XX/XY /XXXX/XY /O/XY /XXX/XY	/XX/XXYY /XXXX/XXYY /O/XXYY /XXX/XXYY	/XX/XXY /XXXX/XXY /O/XXY /XXX/XXY

the principle that masculinization requires the presence of a fetal testicular hormone. Primary amenorrhea, lack of secondary sex development (breasts), and elevated urinary gonadotropins are secondary to the absence of estrogen.

XXX 47 CHROMOSOMES "SUPERFEMALE"

"Superfemale" is a term derived from *Drosophila* studies in which non-disjunction of the x chromosome was noted to produce fruit flies with three x chromosomes (xxx) (24). Jacobs *et al.* were the first to describe a human female with 47 chromosomes (xxx combination) (25). This 35 year old patient demonstrated underdeveloped breasts, infantile internal and external genitalia, and deficient ovarian follicle formation with a "precocious menopause" at 19 years of age. Another xxx female, who is still menstruating at the age of 21, will be reported by the same group (26). Non-disjunction during the first maturation division can produce an xxx individual by the union of a non-disjunctive /xx/ ovum with a normal x sperm (Fig. I and Table I).

XXY—47 CHROMOSOME—KLINEFELTER'S SYNDROME

The clinical picture of the patient with Klinefelter's syndrome (27) includes small testes (primary micro-orchidism), (28) azoospermia and elevated urinary gonadotropins with variable features of eunuchoidism, gynecomastia and mental deficiency (29). Recent data on incidence indicate that this syndrome is more common than originally believed, and has an important role in male infertility (29, 30). Twelve patients with chromatin-positive Klinefelter's syndrome have demonstrated chromosome counts of 47, including an xxy combination (7, 8, 31-34). The presence of the y chromosome in these patients is apparently strongly male determining, and by evoking testes formation (although dysgenetic) there is enough fetal testicular hormone to produce a male phenotype (32).

The origin of the xxy chromosome combination in these patients is believed to be due to non-disjunction of the sex chromosomes in the developing sperm or ovum (4). Color blindness studies tend to indicate that maternal non-disjunction (xx) is likely in these patients, but it is probable that maternal and paternal defects can be responsible just as in the chromatin-negative Turner's syndrome individual (4). Therefore a patient with an xxy Klinefelter's syndrome could be produced by union between a non-disjunctive [xx] ovum and a normal y sperm, or between a normal /x/ ovum and a non-disjunctive xy sperm (/xx/y or /x/xy) due to non-disjunction in the first maturation division (Fig. I and Table I).

POTENTIAL SEX CHROMOSOME COMBINATIONS

All of the known human abnormalities of sex chromosome number (xo, xxy, xxx) can be accounted for by non-disjunction at the first maturation division. The hypothetical possibility of fertilization of a non-disjunctive ovum (/xx/) by a non-disjunctive xy sperm could lead to a potentially viable individual with an xx xy constitution (48 chromosomes). A mongol child with Klinefelter's syndrome has been described with 48 chromosomes (xxy and an additional small autosome of the size which has been previously noted in mongolism, *vide infra*)

lending support to the potential viability of an $xxxy$ individual, since it has been proved that the xxx combination need not be lethal (31). The clinical picture of an $xxxy$ patient may be an accentuation of the features characteristic of Klinefelter's syndrome. Whether non-disjunction may also occur at the second maturation division is uncertain, but the potential chromosome combinations are listed (Fig. 1 and Table I). The known abnormal chromosomal combinations (xo , xxY , xxx) are also seen in this group. The combinations of xYY , $/x'xxY$, $/x/xxYY$ and $/x/xYY$, which have not as yet been described in humans, may theoretically be viable. Though there is no evidence in man that combinations exceeding three x chromosomes ($/xx/xx$, $/xxxx/x$ and $/xxxx Y$) would be viable, such a combination ($xxxx$) has been described in *Drosophila* (35). The possibility of a non-disjunctive sperm fertilizing a non-disjunctive ovum, with each being the product of non-disjunction in the second maturation division would be exceedingly rare, but the mechanisms and combinations of sex chromosomes are listed (Fig. 1 and Table I).

MOSAIC PATTERNS

A mosaic pattern is the term describing a combination of cells which contain a different number of chromosomes in the same individual. Non-disjunction of a sex chromosome during cleavage of the zygote could produce an individual with two differing clones (or progeny of a single cell) (36).

Five patients with gonadal dysgenesis have been described with chromosomal counts (36) or skin chromatin studies (37) suggestive of an $xo-xx$ mosaic. Ford (36) has postulated that these individuals develop from xo zygotes (36). Non-disjunction in an xo embryo producing xx and oo cells, would allow the xx cells to multiply because of the normal genetic constitution, whereas an oo cell is probably nonviable. Simple loss of an x chromosome during mitosis of an xx zygote could also be a mechanism of producing an $xo-xx$ mosaic. An individual with an $xo-xxx$ mosaic will be reported by Court Brown and his group (26). Non-disjunction in an xx zygote at the first mitotic division could produce this combination.

A mosaic pattern containing two groups of cells has been found in one individual with Klinefelter's syndrome ($xx-xxY$) (32). Loss of a daughter y chromosome during mitosis of an xxY zygote could yield a clone of xx cells and a mosaic of this type (36). Similarly, loss of a y chromosome during mitosis of an xy zygote could produce an $xy-xo$ mosaic individual. Two patients have been described with a male pseudohermaphrodite appearance, a dysgenetic testis on one side, and a vestigial streak (38) or an undifferentiated gonad on the other side (39). Future chromosomal studies on such patients will determine whether the clinical picture described is a manifestation of an $xy-xo$ mosaic.

NON-DISJUNCTION OF THE AUTOSOMES

Abnormalities in the number of somatic chromosomes (autosomes) have been found associated with various congenital malformations not involving the sexual

apparatus or its function. Early studies of mongols revealed that they possessed an extra small autosome, but a normal complement of sex chromosomes, giving them a total of 47 chromosomes (40, 41). Non-disjunction during maturation division is believed to be the cause of trisomy of the autosome in this condition (42). Because of the known relationship of increasing maternal age to the incidence of mongolism, the fault may lie in the process of oogenesis (42). A uniform system of numbering the various chromosome pairs by all investigators in this field is now being evolved so that confusion as to which chromosome pair is trisomic may be avoided. Edwards *et al.* (43) and Patau *et al.* (44) independently found that when an extra autosome appeared associated with certain other pairs, congenital anomalies were found (abnormal facies, webbing of the neck, congenital heart disease, cerebral defect, polydactyly, simian creases, "trigger thumbs" and various minor defects). The ultimate possibility of an extra chromosome associated with all 22 pairs of autosomes and the sex chromosomes has been described by Böök and Santesson (22 triploids + an xxy complex 69 chromosomes) (45). This latter observation suggests that an ovum, non-disjunctive for all the chromosomes was fertilized by a normal y containing sperm. The patient, a one year old male, has nonspecific anomalies (multiple lipomatosis, shortness of stature, delayed bone development).

The study of autosomic duplication is still in the stage of collection of data. Many more cases must be documented before one will be able to predict which autosome group is associated with a particular anomaly. The case of Böök demonstrates that duplication of any one particular chromosome need not cause any specific anomaly, since the entire genetic balance of all the chromosomes must be considered. Indeed, the mere presence of an extra chromosome may be associated with apparently normal structure and function as is seen in the case of the normal appearing father of a mongol boy reported by Fraccaro *et al.* (46). The father possessed 47 chromosomes (an extra autosome), while the mongol boy demonstrated 46 chromosomes. Polani *et al.* independently described a mongol girl with 46 chromosomes (42). While the total number of chromosomes in these two mongols was 46 there was evidence, on a histological basis, of a translocation occurring between certain autosomes in Polani's case and either translocation or a combination of trisomy and monosomy for two different autosomes in Fraccaro's case. Evidently, various chromosomal aberrations may cause a similar clinical syndrome, *i.e.* mongolism. The subject of sex chromosomal aberrations (deletion of sex genes, crossover or translocation of sex genes, gene mutations) which may affect gonadal development is discussed elsewhere as a unified theory for the etiology of congenital gonadal defects (47, 48).

SUMMARY

A. Non-disjunction of the sex chromosomes, during the development of the mature sperm or ovum, produces the more commonly recognized forms of Turner's syndrome xo, "Superfemale" syndrome xxx, and Klinefelter's syndrome xxy. The other potential sex chromosome combinations, which have not as yet been described in the literature, are tabulated and discussed.

B. Non-disjunction in the zygote, or simple loss of a sex chromosome during mitosis of the zygote, may give rise to mosaic patterns of XO-XX, XO-XXX, XX-XXY and XY-XO in a few individuals.

C. Non-disjunction of certain autosomes may give rise to characteristic syndromes, *e.g.* mongolism, to nonspecific congenital anomalies which may become characteristic syndromes in the future, or to no congenital anomalies, depending upon which autosome is involved and the degree of genetic imbalance produced.

ADDENDUM

Since this paper was submitted, Drs. Ferguson-Smith and Johnston have reported two patients with an XXXY sex chromosome combination at the annual meeting of the Association of American Physicians in Atlantic City (May 1960). These patients had severe mental retardation and small testes; one patient had gynecomastia. They suggested that non-disjunction occurring during formation of the germ cells in both parents is the "simplest explanation though not necessarily the most probable," for this syndrome, resulting in the fertilization of an XX ovum by an XY sperm. The same investigators also described three presumed cases of the XXX syndrome.

The study group which met to formulate an agreed system of nomenclature for human chromosomes has published a standard nomenclature in *Lancet* I, 1063, 1960.

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THE RADIOACTIVE (I^{131}) ROSE BENGAL TEST OF LIVER FUNCTION

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Rose Bengal, the potassium salt of tetrachlortetraiodofluorescein, is a dye which was introduced in 1923 to detect disturbances of liver function (1). Its general purposes and limitations are similar to bromsulphthalein, but certain difficulties in measuring its removal by the liver from the blood have prevented its routine use. However, recently, Taplin, Meredith and Kade, by replacing the stable iodine atoms with radioactive iodine (I^{131}) in the Rose Bengal molecule, have developed a method of utilizing the substance in the study of liver disease (2).

After intravenous injection, the dye is cleared from the blood exponentially, independent of its concentration in the plasma. The parenchymal cells of the liver take up the dye which is then excreted through the biliary tract into the intestine and eliminated in the feces. There is no enterohepatic circulation. During the time in which the radioactive dye is in the liver, measurement of the rate of uptake and excretion is carried out by means of a scintillation counter, placed over the liver.

Taplin *et al.*, in a series of experiments with normal rabbits found a substantial uptake followed by prompt excretion (2). If the animals were poisoned by carbon tetrachloride, diminished uptake and delayed excretion reflected liver damage. Following ligation of the common bile duct, rapid uptake and delayed excretion were noted.

The findings in each of the three groups of animals were used as a guide to the results in normal humans, in patients with hepatocellular disease and with obstructive jaundice. Patients without liver disease showed prompt uptake and rapid excretion. Those with cirrhosis and hepatitis had delayed uptake and slow excretion, the extent of delay coinciding with the severity of the disease. Persons with obstructive jaundice showed good uptake and delayed excretion.

Based on these experiences, the radioactive Rose Bengal test was advocated as a test of liver function. Special advantages of the test included sensitivity, safety in the presence of biliary tract obstruction, information about patency of the biliary tract and liver circulation, and the elimination of repeated venipunctures and blood studies.

The original methods of Taplin recorded the uptake and excretion for each patient in counts per minute and required comparison of each patient's curve with a number of normal curves. These analyses were subject to many variables, such as the size of the liver, its position in relation to the counter and the thickness of the chest wall. In order to simplify analysis, Lowenstein resolved the

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measurements curve into two components, one representing uptake and the other excretion (3). A correction could be made on the uptake curve for the amount of dye that had been taken up and excreted. As both uptake and excretion took place logarithmically with time, the uptake and excretion curves were straight lines, when plotted on semi-logarithmic paper; and their slopes could be expressed as whole numbers, the half-uptake time (t_u) and the half excretion time (t_e). Lowenstein analyzed 42 curves of Taplin's patients and 28 of his own. He was able to show a range of values for normal patients, a second group indicating delayed uptake and slightly delayed excretion with hepatocellular damage, and a third with markedly delayed excretion in patients with obstructive jaundice.

MATERIAL

In an effort to evaluate this test, 27 patients from the medical and surgical wards and the liver clinic of The Mount Sinai Hospital were studied. The clinical and pathological diagnoses, as well as pertinent laboratory data obtained at approximately the same date that the Rose Bengal test was performed, are presented in Table I.

TECHNIQUE

Five microcuries of I^{131} in 1 to 2 cc Rose Bengal were rapidly injected intravenously. A scintillation counter placed over the liver and directed away from the gallbladder area was used to detect gamma ray emission. Radioactivity was counted and recorded in a sealing circuit, at frequent regular intervals for a period of at least ninety minutes.

The curve of the activity (expressed in counts per minute) was plotted, as the ordinate, on semi-logarithmic paper, *versus* time. From this graph, the half-uptake time (t_u), and the half excretion time (t_e) were obtained, according to the method of Lowenstein (3). A set of graphs depicts the following: Fig. 1, a normal uptake and a normal excretion; Fig. 2, a delayed uptake and normal excretion; Fig. 3, a normal uptake with delayed excretion.

RESULTS

Normal subjects: There were nine patients included in the group in which there was no clinical suspicion of liver disease. Case 6 had just recovered from a fever due to a severe respiratory infection, presumably viral, and the elevated (t_e) might have been caused by a "reactive hepatitis". Unfortunately, no other evaluation of liver function was obtained at the time of this hospitalization. If we exclude Case 6, we find that the average uptake half-time (t_u) was 8.0 minutes with a range of 5 to 12 minutes. The average excretion half-time (t_e) was 126 minutes and the range 66 to 176 minutes.

OBSTRUCTIVE JAUNDICE

Three patients, all icteric, were studied. Case 10 had undergone removal of a cystic duct stone impinging on the choledocus after one week of icterus. Despite

TABLE I
Summary of All Data on Each Patient

Pt.	Clinical Diagnosis	Pathologic Diagnosis	Rose Bengal Test		Blood Tests										
			T _{1/2} U	T _{1/2} E	ISP	Total Bil.	Direct Bil.	Alb.	Glob.	Muco-protein	scor	Alk. Phost.	Cho-lest.	Ceph. Floa.	Thym. Turb.
1.	No liver disease (Pa- rotid Cystadenoma)		9	115				3.9	3.2						
2.	No liver disease (Hook- worm Infestation)		5½	66		0.4	0.2	4.2	2.8	36.0		8.5	155	1+	
3.	No liver disease (Mucocele of Ap- pendix)		7	113											
4.	No liver disease (Anal Fissure)		6	110											
5.	No liver disease (Duo- denal Ulcer)		9	124								5.3		Neg.	
6.	No liver disease (Up- per Resp. Inf.)		12	238				4.6	3.0				190		
7.	No liver disease (He- mangioma of Tongue)		12	90											
8.	No liver disease (Colonic Polyp)		5	176				3.9	3.1			4.7		1+	
9.	No liver disease (In- guinal Hernia)		7	102				4.1	2.6						Neg.
10.	Cholelithiasis	Cystic duct stone (Postop)	9	114		3.0	0.2	4.0	2.8	79.4	165	15.9	200	2+	
11.	Common bile duct carcinoma	Common bile duct carcinoma (Postop)	22	366		16.1	8.7	2.9	3.3			15.3		1+	1.4
12.	Primary biliary cir- rhosis	Biliary Cirrhosis	14½	366		3.7	1.7	2.7	4.4	38		32.8	208	2+	

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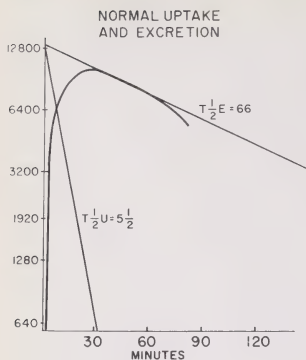


FIG. 1

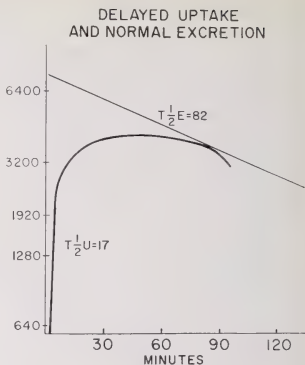


FIG. 2

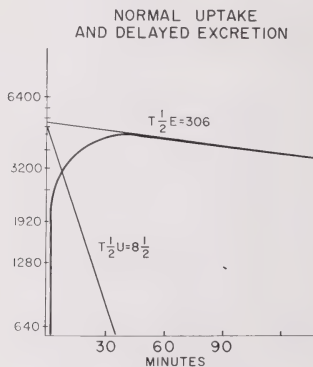


FIG. 3

persistence of icterus, the uptake and excretion of the radioactive material was normal, two weeks after surgery. Subsequently, the patient's icterus subsided and cholangiography revealed no residual calculi.

After several weeks of icterus, operation in Case 11 resulted in a choledochoduodenostomy to by-pass a carcinoma of the common duct. Four weeks following surgery, he was still quite jaundiced, although his serum bilirubin was gradually returning to normal. At this time, the radioactive dye study revealed slightly delayed uptake and moderately prolonged excretion.

The third patient, Case 12, had long standing icterus with liver disease show-

ing features of both primary and secondary biliary cirrhosis. Liver biopsy revealed intrahepatic cholestasis and early cholangiolitic cirrhosis. Analysis of the Rose Bengal test revealed slight prolongation of the (tu) and moderate prolongation of the (te).

Since excretion time has been considered by others to be an important manifestation of obstruction we tried to correlate it with one of the more common indicators of obstruction, the serum alkaline phosphatase. The first case (No. 10) had normal excretion with slightly elevated serum alkaline phosphatase. The second (No. 11) had moderate prolongation of excretion and the highest enzyme value in the series (153 King-Armstrong units). The same excretion time was found in the patient with cholangiolitic cirrhosis who showed a serum alkaline phosphatase of 32.8 King-Armstrong units.

HEPATOCELLULAR DISEASE

Ten patients were studied. Of three patients with viral hepatitis one showed delayed uptake and markedly delayed excretion. Another had slowing of uptake and normal excretion. The third demonstrated a normal uptake and moderately prolonged excretion.

Three patients with portal cirrhosis were studied. One of these, had a superimposed multicentric hepatoma. Uptake was slightly prolonged and excretion was markedly delayed, the slowest excretion time of all cases. One patient, with clinical and laboratory evidence of serious liver dysfunction showed a normal uptake and moderately prolonged excretion. A third patient, in whom liver biopsy at the time of jaundice, four months before the test, showed cirrhosis, had a normal uptake and excretion. This coincided with clinical improvement and absence of disturbance in other hepatic function tests other than slight globulin elevation.

One patient with periportal fibrosis and with fatty infiltration of the liver as demonstrated by biopsy, was studied four weeks after disappearance of jaundice. Radioactive Rose Bengal uptake and excretion were normal as were most chemical tests of liver function. The serum glutamic oxaloacetic transaminase remained slightly elevated at the time of the radioactive dye test.

In a patient with hepatosplenomegaly of unknown etiology (normal liver seen on needle biopsy specimen), uptake was normal but excretion was markedly delayed. Bromsulphthalein retention was 33.5 per cent and serum alkaline phosphatase 7.4 King-Armstrong units. In this case, there would seem to be no correlation between uptake time and BSP retention, and between excretion time and serum alkaline phosphatase.

One patient, with hepatic schistosomiasis, manifested by dense periportal fibrosis, had delayed uptake but normal excretion. This pattern was also seen in another patient, in whom surgery revealed a large solitary hemangioma of the liver.

DUBIN-JOHNSON SYNDROME

Five members of one family with chronic idiopathic jaundice with unidentified pigment in the liver cell were studied. The diagnosis was verified by needle biopsy.

Normal uptake and excretion was observed in one patient, who had 25 per cent bromsulphthalein retention. Normal uptake and slightly delayed excretion were present in a second, normal uptake and moderately delayed excretion in a third, normal uptake and markedly delayed excretion in a fourth, and slightly prolonged uptake and moderately delayed excretion in a fifth.

DISCUSSION

After an intravenous injection, clearance of Rose Bengal from the blood takes place exponentially, irrespective of the plasma concentration. There is no evidence of extrahepatic removal of the dye by the kidney, as occurs with bromsulphthalein. Following extraction from the circulation, the dye is excreted by the liver through the biliary tree into the duodenum. There does not appear to be any enterohepatic circulation (2). The removal of the dye by the liver appears to be a function of the polygonal cells almost exclusively. This is evidenced by direct study of fluorescence of these cells (5). Proof that the liver cell is responsible for the handling of Rose Bengal is shown by the fact that reticuloendothelial blockade (produced by such procedures as intravenous injection of colloidal thorium oxide, india ink, hemolyzed erythrocytes and gelatin, or by intensive irradiation), does not appear to produce any abnormality in the uptake excretion patterns (2).

The value of this test to the clinician appears to be a controversial subject. Before the introduction of the radioactive dye, the use of Rose Bengal had been discontinued and had been replaced by the BSP test. The latter is a more sensitive parameter of hepatic function, as shown by Monroe and Hopper who contrasted results of nonradioactive Rose Bengal tests and BSP tests (6). They studied 24 patients with hepatic diseases and noted that ten patients had abnormal BSP tests and normal Rose Bengal tests, but not one had an abnormal Rose Bengal test and a normal BSP test.

The originators of the radioactive Rose Bengal test have reported quite enthusiastically on their results. They consider it to be the most sensitive specific test for hepatic parenchymal cell function. *

Their conclusions have been supported by Marshall and Kozoll (8) and by Blahd and Nordyke (9). Brown and Glasser (10) and Rosenberg, Lee and Martignoni (11) were not as enthusiastic. The latter group reported a normal Rose Bengal test in 2 of 12 patients with active hepatic disease and abnormal function tests, and in 7 of 8 patients with minimal hepatic disease. Brown and Glasser reported delayed uptake and delayed excretion in patients with obstructive jaundice, cirrhosis and chlorpromazine jaundice, and concluded that the test did not aid in the differential diagnosis of jaundice (10). A recent report by Moertel and Owen indicates many deficiencies in the test (12). They noted a normal uptake in eight of 19 patients with liver disease including five with cirrhosis, one with hemochromatosis, and two with metastatic malignancy. The excretion half-time, did not serve to distinguish between the control group and the 19 patients with liver disease. Prior to this, Snell *et al.* had reported that their experience had revealed normal uptake and moderately prolonged excretion

with hepatic metastases, normal uptake and slightly prolonged excretion in active hepatitis, prolonged uptake and moderately prolonged excretion in "nutritional" cirrhosis, moderate prolongation of uptake and markedly delayed excretion in biliary cirrhosis, and marked prolongation of uptake and marked delay in excretion in partial common duct obstruction (13).

The variations noted in all preceding reports, together with our own data, suggest that the radioactive Rose Bengal test does not give consistent findings in any specific group of liver affections. Whereas it is tempting to conclude that delayed uptake and delay in excretion may be characteristic of liver disease, it is obvious that the same results may be found in patients with obstructive biliary tract disease. Furthermore, the reports of Rosenberg *et al.* (11) and Moertel and Owen (12), as well as our own results, warrant the inference that the test does not help in recognizing mild or inactive forms of liver disease. The claim that the test is more convenient for the patient than other hepatic function tests appears to rest on the need for but one venipuncture. This would appear to be outweighed by the fact that the patient must be practically immobilized during the time of the test. It would seem that the test has limited value in clinical study.

SUMMARY

Experiences are reported with the radioactive Rose Bengal test in the evaluation of 27 patients of whom 18 had liver disease.

The uptake and excretion of the dye tends to become abnormal in the presence of liver disease. However, a normal pattern may be observed in those patients with a minimal inactive hepatic dysfunction. In our limited experience, this test did not appear to be of help in characterizing any type of hepatocellular disease nor in distinguishing hepatocellular from obstructive jaundice.

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CASE REPORT OF AURICULAR FIBRILLATION FOLLOWING THE USE OF IMIPRAMINE (TOFRANIL)^{*}

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Imipramine* (N-(3' dimethylamino-propyl-iminodibenzyl hydrochloride) is a new drug that is beginning to be widely used for its antidepressant action. Toxic reactions include tremors of the extremities, sweating, dizziness, skin eruptions, urinary frequency, eosinophilia, transient jaundice, nausea, vomiting and a mild Parkinsonian-like syndrome. Orthostatic hypotension has been observed and substantial reductions of hypertensive blood pressures may occur (1, 2, 3, 4). Three cases of fatalities occurring during imipramine therapy have been reported (1, 4, 5).

We recently observed a patient under treatment with Imipramine in whom a sudden onset of auricular fibrillation was coincident with an increase in dosage.

CASE REPORT

A 54 year old clerical worker was admitted to the psychiatric ward of The Mount Sinai Hospital on August 27, 1959 with a history of intermittent depression of two years duration, becoming constant and incapacitating four weeks prior to admission. On admission the patient appeared agitated, confused, restless and talked of killing himself because of his unworthiness and because of his pessimistic outlook for the future. The past history disclosed that his illness was first noticed two years prior to admission when the patient was involved in an auto accident which destroyed his car, but caused him no discernible bodily harm. He continued his trip by plane, but felt extremely weak when he arrived at his destination. Due to this weakness and because of a history of a myocardial infarction at the age of 34, he was hospitalized. He was worked up for evidence of cardiac disease and his general condition was evaluated. The patient was discharged after five days without any evidence of heart disease. Since that time the patient had felt intermittently depressed and had been seen by many physicians. On two occasions he was given "tranquilizers", but they seemed to increase his depression, and were discontinued. The patient was diagnosed at The Mount Sinai Hospital as a mild depressive reaction in a passive dependent personality.

Physical examination revealed a well developed, well nourished male, weighing 162 pounds, 5 feet 6 inches in height. The temperature was 98.4 F, the pulse 88, the blood pressure 104/70, and the respiration 20. The heart was not enlarged to percussion, and no murmurs were heard. A point of maximum impulse was not palpable. The lung fields were clear to auscultation. All physical findings were within normal limits.

X-rays of the chest revealed prominent pulmonary markings bilaterally

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* Tofranil[®] Geigy

distorted. The heart appeared to be at the upper limits of normal in its transverse diameter. The mediastinum was within normal limits. Electrocardiogram showed a normal sinus rhythm, left axis deviation, wide Q wave in leads 1, aV, and V_1 to V_3 . These changes were considered indicative of previous anterior wall infarction. The hemoglobin was 17.3 Gm per 100 ml and the white cell count was 6600 with a normal differential. Specific gravity of the urine was 1.028. Tests for albumin, sugar, acetone and bile were negative. The centrifuged urinary sediment contained occasional red blood cells and a few calcium oxalate crystals but no casts.

Two days after admission the patient was started on Imipramine 25 mg t.i.d., after blood pressures taken first in the recumbent, sitting and standing positions. The patient was allowed to lie on a couch in a quiet room for five minutes. A sphigomomanometer was then applied and a pressure taken. He then sat on the couch and another blood pressure was quickly taken. After this he stood up and the final determination was made. The control blood pressures lying down were 110/78, sitting 100/78, and standing 90/78 mm of Hg, respectively.

The patient received 75 mg of Imipramine for eight days, followed successively by 100 mg per day for five days, 150 mg for one day, and 175 mg for one day. The dosage was raised because no effects were seen at the lower dosages, and we were aiming at a dosage of 200 mg a day, but the sudden onset of symptoms at 175 mg per day caused a discontinuance of the drug.

Fifteen days after starting drug therapy the patient reported the sudden onset of palpitations, a feeling of being "chilly and warm at the same time", and profuse sweating and weakness were noted. The patient never had any similar symptoms. Supine blood pressure was 92/50, sitting blood pressure 90/50, and standing blood pressure 90/50 mm of Hg, respectively. The pulse was irregular at 120 per minute. No chest pain was present and the lungs were clear. An electrocardiogram revealed auricular fibrillation with no evidence of a fresh infarct.

Imipramine was discontinued. The patient was given mephentermine sulfate, and was placed on digitalis and quinidine. The auricular fibrillation disappeared the next day, and never recurred. The patient was continued on digitalis for five days and quinidine for six days after the onset of symptoms. The laboratory tests revealed continuously high hemoglobin concentrations (16.8-8.3 Gm per 100 ml) throughout the patient's hospitalization with no other atypical findings. This finding was diagnosed as a manifestation of stress polycythemia.

DISCUSSION

Three cases of fatality following the use of Imipramine have been heretofore described. Mality, Wilkins and Escover reported an anterior wall infarct in a patient who received 75 mg for seven days (4). Lehman, Cahn and De Verleuil felt that a fatal myocardial infarction may possibly have been related to the Tofranil* which the patient was being given although there was no direct evidence of this relation (1). Freyhan reported, "One 77 year old female died in the fourth week of treatment while receiving 227 mg Tofranil* per day" (5). Death was attributed to coronary occlusion, but autopsy was not permitted.

Experimental work with dogs has demonstrated that Imipramine "blocks" normal bradycardia resulting from stimulation of the peripheral end of the vagus with a fall in blood pressure (6). Clinical experience by other workers has demonstrated hypotension and syncope, and one case of dyspnea and cyanosis that was promptly relieved by a reduction in dosage (1).

In our case, the striking drop in diastolic blood pressure, weakness, dizziness, and cardiac irregularity in a patient who never had similar symptoms after his infarction 20 years previously, as well as the absence of any emotionally provoking stimulus discernible from the intensive psychotherapy that the patient received throughout his hospitalization, lead us to believe that Imipramine was responsible for the auricular fibrillation that occurred.

A possible mechanism of this cardiovascular effort may be the vagal blocking action that has already been recognized. Its nonuniform manifestations may reflect the underlying state of the heart, people with less cardiac reserve being more prone to its effects. The drug must be carefully regulated, and cases selected with previous cardiac pathology well evaluated.

SUMMARY

A case of auricular fibrillation after administration of a new antidepressant drug, Tofranil[®], is presented. Other cases of myocardial damage in which Tofranil[®] was administered have been reviewed. Speculation concerning the possible dangers of this medication in cases with a previous history of heart disease are discussed, along with possible mechanism.

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THE USE OF LONG-ACTING QUINIDINE GLUCONATE IN THE MANAGEMENT OF ATRIAL FIBRILLATION

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Quinidine sulfate, administered orally, is the preparation generally employed for the conversion of atrial fibrillation to sinus rhythm, for maintenance of sinus rhythm and for the prevention of attacks of paroxysmal atrial fibrillation. Maintenance doses of 0.4 Gm given four times daily have been found to give adequate therapeutic serum levels (1). With the aim of simplifying the maintenance treatment, long-acting quinidine preparations have been studied in the past (2, 3).

Recently, long-acting quinidine gluconate has been introduced and found to result in effective and sustained blood levels (4). We have sought to compare the action of this preparation in normals with that of quinidine sulfate and to evaluate its efficacy in maintaining normal sinus rhythm in patients with previous atrial fibrillation.

MATERIAL AND METHODS

Five normal subjects were given a single dose of quinidine sulfate and two days later a dose of long-acting quinidine gluconate; each dose was equivalent to one Gm of quinidine base. The calculation is based on an 82.86 per cent content of quinidine base in quinidine sulfate as compared to 62.3 per cent quinidine base in quinidine gluconate. Serum quinidine levels were determined at 1, 3, 5¹/₂, 8, 12 and 24 hours after the administration by the method of Brodie and Udenfriend (5).

Twelve patients with atrial fibrillation were treated with long-acting quinidine gluconate. Five patients had inactive rheumatic heart disease and four arteriosclerotic heart disease. Eight patients had established atrial fibrillation and four paroxysmal atrial fibrillation. In all patients with established atrial fibrillation, conversion to sinus rhythm was effected by quinidine sulfate. Long-acting quinidine gluconate was not employed for conversion of established atrial fibrillation, in order to avoid prolonged excessive serum levels of quinidine if cardiac toxicity should ensue. However, long-acting quinidine gluconate was administered for maintenance of sinus rhythm after the latter was established. In two of the four patients with paroxysmal atrial fibrillation, quinidine sulfate was employed to prevent recurrences and later long-acting quinidine gluconate was substituted. In one of the four, only long-acting quinidine gluconate was administered and in one quinidine sulfate and later a combination of quinidine sulfate and long-acting quinidine gluconate. Blood samples were collected at 8:30 a.m., one half hour before the first dose of the day, in order to demonstrate the minimal serum quinidine level from the previous day's treatment.

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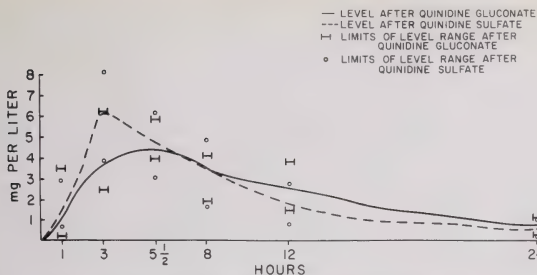


FIG. 1. Curves of mean serum quinidine levels in five normal subjects after administration of one Gm of quinidine base as quinidine sulfate and two days later as long-acting quinidine gluconate.

RESULTS

The mean serum quinidine levels attained in the group of normal subjects are shown in Fig. 1. After quinidine sulfate, a peak level of six mg per liter is reached within three hours and the level falls to less than one mg per liter in 24 hours. After long-acting quinidine gluconate, the serum quinidine level ascends at a slower rate reaching four mg per liter after three hours and a peak of 4.5 mg per liter after 5½ hours, following which the level falls to a mean level of less than one mg per liter in 24 hours. The mean level is similar with both preparations six to eight hours after the administration. At 12 hours after the administration, the serum quinidine levels are significantly higher with long-acting quinidine gluconate, ranging from 1.5 to 3.9 mg per liter as compared with levels ranging from 0.8 to 2.8 mg per liter after quinidine sulfate.

Table I lists the twelve patients, showing the type of heart disease, sex, age, the daily maintenance schedule and the minimal serum quinidine levels in successfully treated patients. All patients who had previously established atrial fibrillation remained in sinus rhythm. Seven patients were managed with two doses of long-acting quinidine gluconate daily, one with three doses. In the four patients treated for the prevention of recurrent paroxysmal atrial fibrillation, normal sinus rhythm was maintained in two patients. The treatment was discontinued in the remaining two because of gastrointestinal discomfort following sulfate or gluconate. The minimal serum quinidine level in the successfully treated patients varied between 1.75 and 5 mg per liter. Cases 1, 2, 9, and 10 are described below to illustrate methods of management.

CASE REPORTS

Case 1

B. F. is a 47 year old white female with inactive rheumatic heart disease five years post mitral commissurotomy. She was admitted because of exercise intolerance and fatigue

TABLE I

Twelve Patients Treated with Long-Acting Quinidine Gluconate. Daily Drug Schedule and Minimal Serum Quinidine Levels of Patients Successfully Maintained in Sinus Rhythm

Case No.	Type of Heart Disease	Sex	Age	Daily Drug Schedule	Minimal Serum Quinidine Level (Mg. liter)
1*	Inact. RHD, post mitral valvulotomy	F	47	Q. gluc. 0.6 Gm \times 2	4.1
2*	Inact. RHD, post mitral valvulotomy	M	33	Q. gluc. 0.6 Gm \times 3	3.0
3*	ASHD	M	59	Q. gluc. 0.6 Gm \times 2	2.6
4*	Inact. RHD, mitral-aortic valv. dis.	M	43	Q. gluc. 0.6 Gm \times 2	1.75
5*	ASHD	M	58	Q. gluc. 0.6 Gm \times 2	5.0
6*	Inact. RHD, post mitral valvulotomy	F	44	Q. gluc. 0.6 Gm \times 2	3.3
7*	Inact. RHD, mitral-aortic valv. dis.	M	60	Q. gluc. 0.6 Gm \times 2	3.2
8*	ASHD	M	65	Q. gluc. 0.6 Gm \times 2	4.4
9	Rec. paroxysmal atrial fibrillation	M	76	Q. gluc. 0.45 Gm \times 2	2.6
10	ASHD, rec. paroxysmal atrial fibrillation	M	54	Q. sulf. 0.6 Gm \times 2 Q. gluc. 0.6 Gm	4.2
11	Rec. paroxysmal atrial fibrillation	M	55	Not maintained (G.I. disturbances)	—
12	Rec. paroxysmal atrial fibrillation	M	50	Not maintained (G.I. disturbances)	—

* Established atrial fibrillation converted to sinus rhythm with quinidine sulfate. RHD = Rheumatic heart disease. ASHD = Arteriosclerotic heart disease. Rec. = recurrent.

associated with established atrial fibrillation. One year prior to admission sinus rhythm had been restored by quinidine, but atrial fibrillation recurred when the drug was withdrawn. In the hospital she was digitalized and sinus rhythm restored after ten doses of quinidine sulfate 0.4 Gm given at intervals of six hours at a serum quinidine level of 9.14 mg per liter. After normal sinus rhythm was established, long-acting quinidine gluconate, 0.9 Gm twice daily, was substituted and later reduced to 0.6 Gm twice daily. Sinus rhythm was maintained and the patient's exercise tolerance improved.

Case 2

S. T. is a 33 year old white male admitted because of atrial fibrillation and progressive congestive heart failure of three months duration. The patient had a history of acute rheumatic fever at five years of age and had a mitral commissurotomy three years prior to admission. The patient was digitalized and was converted to sinus rhythm with 2.4 Gm quinidine sulfate. Long-acting quinidine gluconate, 0.6 Gm every eight hours, was substituted and sinus rhythm was maintained. The patient's heart failure improved.

Case 9

B. E. is a 76 year old white male with attacks of paroxysmal atrial fibrillation associated with palpitations, general discomfort and anxiety. During one of the attacks, transient

signs of a cerebrovascular accident developed. The patient was treated with 0.45 Gm of long-acting quinidine gluconate twice daily. Sinus rhythm returned, probably spontaneously, but no further attacks occurred while he continued on long-acting quinidine gluconate.

Case 10

I. K. is a 54 year old white male with arteriosclerotic heart disease and attacks of paroxysmal atrial fibrillation accompanied by chest pain. Quinidine sulfate 0.4 Gm was first administered daily at 9 a.m., 3 p.m., 9 p.m. and 3 a.m. to prevent the recurrent fibrillation, but was unsuccessful. It was observed that most of the attacks occurred in the early morning and at 5:30 p.m. When the dose was increased to 0.6 Gm the patient complained of nausea and diarrhea. Therefore the first two daily doses were maintained at 0.6 Gm quinidine sulfate and the last two doses of quinidine sulfate were replaced by long-acting quinidine gluconate, 0.6 Gm given at 9 p.m., without disturbing gastrointestinal symptoms. The patient remained free of attacks with quinidine sulfate, 0.6 Gm at 9 a.m. and 3 p.m., and long-acting quinidine gluconate, 0.6 Gm at 9 p.m.

DISCUSSION

A comparison of the mean serum quinidine levels in normals after identical doses of quinidine sulfate and long-acting quinidine gluconate, containing one Gm of quinidine base, discloses the steep ascent of the curve after quinidine sulfate, reaching the 6 mg per liter peak after three hours, followed by a rapid descent of the curve towards low levels. Long-acting quinidine gluconate produces a curve with a slower ascent, reaching a peak of 4.5 mg per liter after 5½ hours, and with a slower descent maintains higher levels than quinidine sulfate from eight to twelve hours after the administration. Bellet found a peak quinidine concentration of 4.34 mg per liter 4.8 hours after the administration of one Gm long-acting quinidine gluconate and 2.39 mg per liter after twelve hours, values which correspond to ours (4). The serum quinidine levels obtained in different individuals after the same dose of long-acting quinidine gluconate varied widely as they do with quinidine sulfate. Long-acting quinidine gluconate, having more sustained serum levels which are within therapeutic range up to twelve hours, can be given for maintenance treatment at an interval of twelve hours or at eight hours. There appears to be no advantage in its use at an interval of six hours or less when quinidine sulfate gives good serum levels.

In all our patients with established atrial fibrillation converted to sinus rhythm, long-acting quinidine gluconate was able to maintain the sinus rhythm without any side actions. In all but one of these, this was accomplished with two daily doses and in one case with three daily doses. As a rule, quinidine sulfate must be given four times daily. There is always a problem of the longer interval between the last evening dose and the first morning dose and the danger of recurrence of atrial fibrillation because of the fall in serum quinidine level during the night. Serum quinidine levels determined twelve hours after the evening dose of long-acting quinidine gluconate and before the morning dose, ranged between 1.75 and 5 mg per liter, apparently adequate for the maintenance of sinus rhythm. The usual dosage of long-acting quinidine gluconate was 1.2 Gm daily which is equivalent to 0.94 Gm quinidine sulfate.

In two patients with paroxysmal atrial fibrillation, long-acting quinidine gluconate, like quinidine sulfate, was unsuccessful in preventing recurrent attacks despite maximally tolerated doses. Both with quinidine sulfate and quinidine gluconate, severe gastrointestinal symptoms and associated weakness forced a discontinuation of these drugs. There was no evidence that relatively higher doses of long-acting quinidine gluconate than of quinidine sulfate could be given before intolerable side actions appeared.

In one patient with paroxysmal atrial fibrillation, it was possible to prevent recurrences with only two doses of 0.45 Gm long-acting quinidine gluconate daily. The fourth patient with paroxysmal atrial fibrillation continued to have attacks on quinidine sulfate up to a total of 2.4 Gm in four divided doses, which induced nausea and diarrhea. It was observed that atrial fibrillation was likely to appear in the early morning hours before the patient awoke and in the late afternoon. By giving him 0.6 Gm quinidine sulfate at 9 a.m. and 3 p.m., adequate quinidinization was attained to prevent the evening attacks without disturbing gastrointestinal symptoms, and a single dose of long-acting quinidine gluconate 0.6 Gm carried him through the night and early morning. Thus his total gram dosage was less than with quinidine sulfate alone and no night dose had to be given.

In this study long-acting quinidine gluconate was generally substituted after the effective maintenance dosage had been established with quinidine sulfate. This followed the conversion of established atrial fibrillation to sinus rhythm with quinidine sulfate and the administration of one-half or two-thirds of the amount of quinidine sulfate used for daily maintenance.

SUMMARY

A. Long-acting quinidine gluconate was studied to determine the serum levels of quinidine and its effectiveness in the management of atrial fibrillation.

B. Five normals were given one Gm of quinidine base as quinidine sulfate and their serum levels after 1, 3, 5¹/₂, 8, 12 and 24 hours were compared to the levels after the same dose administered as long-acting quinidine gluconate. The peak serum quinidine level after long-acting quinidine gluconate was lower than after quinidine sulfate, but the levels descended more slowly and eight to twelve hours after the administration, definitely higher serum levels were maintained by long-acting quinidine gluconate.

C. Long-acting quinidine gluconate was given to eight patients with previously established atrial fibrillation after conversion to sinus rhythm. This was successful in maintaining sinus rhythm in all the cases, usually with a dose of 0.6 Gm twice daily. The serum quinidine level twelve hours after the evening dose ranged between 1.75 and 5 mg per liter.

D. Of four patients with paroxysmal atrial fibrillation, long-acting quinidine gluconate prevented further attacks in two and failed in two others in whom quinidine sulfate had likewise failed.

E. No side actions were observed in the maintenance of the cases with previously established atrial fibrillation. In two cases with paroxysmal atrial

fibrillation where treatment had to be discontinued, the cause was gastrointestinal discomfort and weakness.

F. Long-acting quinidine gluconate has been found to produce more sustained serum quinidine levels than quinidine sulfate and to be an effective drug for the maintenance of sinus rhythm in patients who previously had established atrial fibrillation, and for the prevention of recurrent paroxysmal atrial fibrillation.

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VITAMIN LEVELS IN CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS. II.*

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We have investigated the cerebrospinal fluid (CSF) level of vitamins in patients suffering from a number of neurological diseases, especially patients with demyelinating disease. We have previously reported (1) our observations in a group of neurological patients, in whom we determined by our microbiological assay methods (2-6) the vitamin B₁₂ and folic acid concentration in CSF and serum. The present study extends and amplifies these observations.

RESULTS

The present survey of the vitamin B₁₂ content in 420 unselected neurological cases shows a relatively high percentage of values above the range found in normal subjects. (It should be noted that none of our patients received any vitamin therapy.)

The incidence of high values seems to be concentrated in patients with multiple sclerosis. As shown in Table I, fourteen of 41 cases of multiple sclerosis had a vitamin B₁₂ content of CSF higher than 30 $\mu\text{g}/\text{ml}$. An equal proportion (but not necessarily the same cases) showed a blood content of vitamin B₁₂ above 1000 $\mu\text{g}/\text{ml}$. The situation with folic acid was even more striking. This vitamin was found elevated in 34 of 42 cases of multiple sclerosis. A smaller proportion of multiple sclerosis patients showed increases of thiamine in the spinal fluid to twice the upper normal limit.

Table II gives a synopsis of vitamin analyses in additional 14 cases of multiple sclerosis, extended to pantothenic acid, folinic acid and thiamine. The pantothenic acid values, although fluctuating, remained within the wide normal range (7). The folic acid values were low in three cases, but higher than normal in four cases. Thiamine values were increased in four cases. A particularly high value of 280 $\text{m}\mu\text{g}/\text{ml}$ was noted in patient J.T., an early case of multiple sclerosis. Three cases showed an increased B₁₂ value. Folinic acid was demonstrable in the CSF of these cases, but its significance in neurologic disease is still questionable. In serum, no folinic acid can be demonstrated by the method used.

DISCUSSION

It is possible that deviations of CSF constituents in multiple sclerosis may be detected only during acute exacerbations. If this be so, the single specimens which we were able to obtain give only a cross-section of an unstable situation,

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TABLE I
Folic Acid and Vitamin B₁₂ in Multiple Sclerosis

Case No.	Folic Acid in CSF $\mu\text{g}/\text{ml}$	B ₁₂ in CSF $\mu\text{g}/\text{ml}$	B ₁₂ in Serum $\mu\mu/\text{ml}$
Normal Controls.....	10-30	0-30	300-1000
118	4000	150	—
211	3000	40	3000
103	2000	110	4800
200	2000	100	3300
88	1900	10	—
234	1500	10	—
229	1500	0	—
287	1000	330	—
179	600	10	800
73	550	70	—
155	500	30	—
254	400	10	1000
143	400	0	—
3	300	50	—
298	300	30	—
250	300	10	1000
43	240	—	—
249	220	10	1000
257	200	30	400
244	200	10	1000
246	200	10	—
32	200	—	—
136	130	70	650
65	130	20	—
72	130	50	—
127	100	40	450
165	70	30	1300
119	60	120	—
262	60	10	1000
261	60	10	600
292	60	10	—
295	40	30	—
278	40	15	1000
140	40	0	220
108	20	70	—
151	20	30	450
152	20	30	—
105	20	5	—
168	20	10	2000
76	10	600	1100
77	10	200	—
174	—	20	1000
175	10	20	—

TABLE II
Vitamins in CSF of Multiple Sclerosis

Multiple Sclerosis Cases	Vitamins				
	Pantothenic Acid ($\mu\mu\text{g/ml}$)	Folic Acid ($\mu\mu\text{g/ml}$)	Folinic Acid ($\mu\mu\text{g/ml}$)	Thiamine ($\mu\mu\text{g/ml}$)	B ₁₂ (Cyanocobalamin) ($\mu\mu\text{g/ml}$)
G.P.	728	14	3	15	40
W.D.	303	27	3	15	20
R.R.	305	1	1	36	80
S.B.	600	23	4.5	15	—
A.P.	1150	35	1	14	20
L.V.	625	40	1	20	20
J.C.	440	9	1	25	20
J.B.	160	8	1	24	—
T.G.	175	15	1	20	10
J.T.	450	20.5	2.5	280	30
W.K.	350	20	3	11	30
T.M.	350	27	2.5	10	10
A.H.	450	46	4	—	30
A.P.	350	32	2	17	40

and the observed incidence of abnormal values is as high as one may expect. It appears to be of considerable significance.

It is not clear whether the abnormal vitamin levels are involved in the causative mechanism of multiple sclerosis or act merely as indicators of changes in the permeability of the blood—CSF barrier.

No correlation with demyelinating disease is obvious in the pantothenic acid content of CSF; the values of this vitamin in CSF show wide fluctuations. (Particularly low values were encountered in a case of lupus erythematosus and in a patient with a tumor with brain metastases.)

Our experience indicates that during exacerbation of multiple sclerosis, these vitamins, in particular B₁₂, are found at high levels. When the acute stages have passed, the vitamin levels return to normal. The significance of these observations remains currently obscure.

SUMMARY

We have studied large groups of patients with neurological disease and have observed a high coincidence of elevated values of vitamin B₁₂, thiamine, and particularly of folic acid in the CSF of patients with demyelinating disease. The values for pantothenic acid in CSF display great fluctuations among unselected neurological patients and require further analysis for interpretation. A table showing the vitamin analysis of the CSF of 14 cases of multiple sclerosis is given.

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COLONIC LESIONS SECONDARY TO ENDOMETRIOSIS

REPORT OF SEVEN CASES

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It is the purpose of this paper to stress the importance of and difficulty in differentiating endometriosis from neoplastic and inflammatory disease as a causative factor of large bowel obstruction. One of the first recognized instances of endometrioma causing an intestinal obstruction was reported in 1909 (1). Since then, periodic reports of this occurrence have appeared in the literature (2 to 17). Our interest in endometriosis causing large bowel obstruction is based on a recent experience with two of the seven cases herein reported. The remaining five cases in this report were taken from the records of patients seen both in the private and ward services at The Mount Sinai Hospital from the years 1938 to 1959. This report is written with the hope that an awareness of the possibility of intestinal obstruction being caused by endometriosis may save a patient from needless radical bowel surgery.

The incidence of colonic involvement by endometriosis reportedly varies from five to forty per cent (3, 10, 18). Paralleling a series of one thousand consecutive colonic resections for carcinoma, two cases presented with an endometrioma of the colon producing large bowel obstruction (19). A statistical study of carcinoma of the colon and rectum showed the incidence in females under fifty years of age to be fifteen per cent (20). In the present study, endometriosis accounted for about one per cent of left-sided intracolonic lesions in women fifty years of age and younger. It is, of course, impossible to deduce from this incidence what the incidence is in the general population, but the figures serve to suggest that endometrial lesions as a factor in large bowel obstruction in women fifty years of age and under appear more frequently than usually considered clinically.

DIAGNOSTIC CRITERIA

In the differential diagnosis of endometriosis of the sigmoid or upper rectum, diverticulitis, amebiasis, colitis, polyps, benign tumors of the colon and carcinoma must be considered.

The correct diagnosis of colonic endometrioma was made preoperatively in two of our seven patients. In one patient, cyclic rectal bleeding indicated the pathology, while in the other patient the radiologist suggested the diagnosis.

Our patients were between 32 to 55 years of age. This is in keeping with most series (2, 3, 5, 15). The average age in our series was about 45 years as compared to 39.5 years noted in a similar study (5). The median age for adenocarcinoma of the descending colon, sigmoid and rectum in females was recently reported to be 58.5 years (26). One patient in this group was four years postmenopausal

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when symptoms of obstruction due to endometrial involvement of the large bowel occurred. Similar cases of almost complete obstruction due to colonic endometriosis after the menopause have been described (4, 5). This fact is not commonly appreciated and further illustrates the diagnostic difficulties.

All but one of the seven patients were married. Only one showed a definite infertility pattern. The occurrence of relative sterility in patients suffering from endometriosis is the common finding (21). Menstrual abnormalities have been reported in as high as 80 per cent of cases with endometriosis in some series (21). Complaints of progressive dysmenorrhea and menstrual irregularities frequently associated with endometriosis were specifically noted in two of the seven cases. Blood in the stool from endometriosis was noted in three cases. In addition, two of these patients had monthly cycles of rectal bleeding at about the time of their menses; in general this is unusual (2, 9). Irregular rectal bleeding associated with colitis and endometriosis was noted in a third patient; the origin of this bleeding was, however, not determined.

The presenting symptoms in our group of patients were referable to the lower gastrointestinal tract. The majority of patients complained of colicky abdominal pains associated with constipation and scybali. One patient presented with cyclic episodes of diarrhea and rectal bleeding. Increasing severity of abdominal symptoms was not present in any of our cases. In other series, however, this diagnostic feature was stressed (5, 15). In more than 50 per cent of their cases, an exacerbation of abdominal symptoms associated with the menstrual period occurred. The obstructive symptoms were intermittent in two of our cases and varied from complete to partial obstruction in the remaining five cases.

Significant weight loss was present in only one of our cases; although it appeared more commonly in another series (5). In view of the latter observation, weight loss *per se* may not be too helpful in the differential diagnosis between endometriosis and carcinoma of the bowel.

Physical examination revealed no abnormalities in two of the seven cases. The most common physical finding to support the diagnosis of endometriosis includes the presence of tenderness, nodularity, or thickening in the cul-de-sac or along the uterosacral ligament (21). This was found in half of our cases. Associated ovarian cysts or ovarian enlargement may be present. The uterus is often retroverted, immobile, and tender to palpation.

RADIOGRAPHY

The roentgenographic appearance of colonic endometrioma may be that of a polypoid or constricting mass, as demonstrated by barium enema examination. In only one case was the true diagnosis suspected on the basis of the barium enema. In four of the cases the lesion appeared to be of a constricting nature; in two of our cases a polypoid defect in the colon was noted. This differs from a recent report in which the roentgenographic defect was most often seen as polypoid (16). In one of the earlier cases of our series, no organic obstruction was seen on x-ray. However, spasm of the sigmoid was present. At autopsy, the colon showed endometriosis in the wall of bowel affected with ulcerative colitis.

In endometriosis causing large bowel obstruction, barium enema will reveal a longer area of stenosis with intact mucosa. In contrast, the mucosa in carcinoma of the bowel is eroded, the constriction is over a shorter length and is usually accompanied by a greater rigidity of the bowel (17). To further aid in the differential diagnosis, it has been suggested to fluoroscope the segment of involved bowel when the patient is menstruating. Tenderness and fixation of the lesion will point to the presence of endometriosis (16, 17).

SIGMOIDOSCOPY

Sigmoidoscopy usually will reveal normal mucosa, as the site of pathology lies in the muscularis and subserosa. When the mucosa is involved, endometriosis of the bowel wall will often be difficult to distinguish on inspection from carcinoma (15). Punch biopsy will often reveal the true nature of the disease (12). Occasionally the biopsy may be misread as carcinoma due to marked desmoplasia and scantiness of endometrial tissue (15). If it is felt that the lesion has been missed, and only normal mucosa is present in the biopsy, further information may be obtained from needle biopsy.

PATHOLOGICAL FEATURES

At laparotomy, the surgeon should make note of specific evidence of gynecological pathology. The presence of pelvic endometriosis may alert him to the benign nature of the condition so that proper therapy may be instituted.

The specimens of endometriosis involving the bowel vary from slightly raised plateaus and polypoid masses to annular lesions. The least involvement may reveal only scattered endometrial implants with scarring and induration of the serosa. With moderate involvement the masses are usually well localized, may resemble carcinoma but are less firm. In cases with extensive involvement, the endometrioma may appear to invade the surrounding pelvic tissues. Frozen section is indicated if there is any difficulty in differentiating between carcinoma and endometriosis.

On sectioning the specimen, the surfaces are glistening and grayish white. Histologically, an intact mucosa is a constant finding, although it may be attenuated and edematous. The characteristic finding is hypertrophy of the muscularis with accompanying inflammatory reaction. The serosal surface is often thickened and nodular. The presence of endometrial stroma confirms the diagnosis.

THERAPY

Much has been written about the problems of therapy of endometriosis. Surgery has long been the method of choice (2, 22). The procedures advocated include oophorectomy, segmental resection or a combination of both. Conservative resection without surgical sterilization has been urged in patients in the reproductive age group with or without subjective symptoms of endometriosis. In older patients, surgical castration with or without temporary colostomy has been advocated. Following surgical castration alone, in a series of patients with

constricting endometriosis of the rectosigmoid, complete restoration of the lumen of the bowel was observed in follow-up barium enema as early as two months later (3).

In cases in which the operation and general condition of the patient presents difficulty, there may be indication for localized x-ray therapy or castration by radiation (9, 23).

Hormone therapy, of many types, seems less useful as definitive therapy (24). A recent report suggests that progesterone induced pseudopregnancy causes softening of the endometrial lesions with ultimate regression in some instances (25). These findings, if confirmed in larger clinical trials, may be an effective adjunct to surgery in the treatment of the large bowel obstructions due to endometriosis.

CASE REPORTS

Case 1

A forty-four year old white parous female was admitted to The Mount Sinai Hospital complaining of pressure on the rectum. There was no significant weight loss, abdominal pain, diarrhea, constipation or melena. Menstrual history was unremarkable except for having undergone a cervical polypectomy one year prior to admission, for irregular bleeding. On rectovaginal examination, a large hard fixed mass displacing the anterior rectal wall and filling the cul-de-sac was noted. The patient was sigmoidoscoped; at six inches a friable hard mass was biopsied. All fragments obtained showed normal rectal mucosa without significant change. A barium enema revealed a marked irregular narrowing with evidence of ulceration of the rectosigmoid area.

At operation the uterus was seen to contain several medium sized fibroids. There was a mass projecting from the posterior surface of the uterus which invaded and involved in a circumferential manner the lower sigmoid colon, producing almost complete obstruction. The right ovary was normal; the left was fairly enlarged and cystic. On the basis that the above finding represented an invasive carcinoma of the rectosigmoid, the patient underwent an abdominal perineal resection, total abdominal hysterectomy, and a left salpingo oophorectomy.

Pathologically, the specimen showed extensive endometriosis of the sigmoid with marked stenosis of the lumen. The mucosal surface was intact but thrown into folds; the muscularis of the adherent sigmoid wall was markedly thickened. On the posterior wall of the rectum slight dimpling and scarring of the mucosa was present. The proximal sigmoid was dilated; its muscularis hypertrophied and mucosa edematous. There was no evidence of carcinoma of the bowel. Glandular tissue was unremarkable. The left ovary contained a corpus luteum cyst.

Case 2

A forty-seven year old mother of four children was admitted to The Mount Sinai Hospital. She complained of recent vaginal staining following a normal menstrual period. Her menses prior to this episode were regular and without evidence of dysmenorrhea. About this time she experienced the insidious onset of constipation with rabbit type stools, intermittent abdominal distention and gas pains. No history of rectal bleeding or diarrhea was obtained. A week later she developed a slightly distended abdomen.

On examination, the uterus was of normal size and shape, not tender and mobile. No masses were noted in the cul-de-sac or lateral quadrants. Cervix smears showed normal estrous effect with no cancer cells present.

Barium enema was compatible with an obstructing lesion of the lower sigmoid. An an-

nular grayish tumor, several centimeters in length, was found. Other lesions consisted of bilateral chocolate cysts imbedded in fibrous tissue and scattered grayish plaques extending into the cul-de-sac. A sigmoid resection and supplementary tube cecostomy was done as it was felt the pathology represented bowel carcinoma associated with endometriosis.

Gross examination of the specimen revealed intact mucosa lining the firm and thickened portion of stenotic bowel. Endometriosis of the sigmoid involving the serosa, muscular and submucosal layers was confirmed on microscopic examination. No malignancy was present.

Follow-up: Following discharge the patient received 2000 r to an area 14 cm in diameter corresponding to the pelvic inlet. The radiation for castration was given over a four week period. About a week following radiation therapy she developed a draining fistula at the site of the tube cecostomy. In addition, she experienced the acute onset of tenesmus, diarrhea, and melena.

Admission sigmoidoscopy revealed a constriction at five inches. The entire mucosa up to five inches was inflamed, friable, and bled easily. Scattered areas of a whitish exudate were present. Also, a superficial anal ulcer was noted. The findings were consistent with either ulcerative colitis or radiation proctitis. In view of the clinical picture the latter seemed to be the most probable diagnosis.

Comment. Cases #1 and #2 illustrate that at the time of laparotomy it is often impossible to differentiate grossly a malignant tumor of the bowel from endometriosis. In Case #1 a biopsy revealed normal rectal mucosa. Because of this report, and in view of the sigmoidoscopic and barium enema findings, further deeper biopsies might have been indicated. For this reason also it may be beneficial to perform a colostomy in order to visualize the mucosa, and take a biopsy under direct vision for frozen section. When the proper diagnosis is made an extensive resection can be replaced by local excision, a temporary colostomy, or castration. Case #2 points up the complication following radiation castration.

Case 3

A fifty-five year old postmenopausal colitis patient was admitted to The Mount Sinai Hospital with a history of increasing constipation and lower abdominal cramps. X-rays taken prior to admission showed an annular lesion involving the midsigmoid with apparently normal mucosa. On the basis of the radiologic findings, a tentative diagnosis of endometriosis was made.

Past history was significant in that the patient underwent a partial hysterectomy, a left salpingo-oophorectomy, and a right salpingectomy for a fibroid uterus four years prior to admission. Physical examination was consistent with a large bowel obstruction but rectovaginal examination was unrevealing.

At laparotomy, an annular lesion of the sigmoid, about an inch in diameter, was noted. The surgeon observed that the lesion did not have the characteristic firmness of bowel carcinoma. No evidence of lymphatic involvement or metastasis was apparent. The right ovary appeared atrophic. The pelvis was devoid of obvious endometrial implants. A segmental resection of sigmoid was performed on the presumptive diagnosis of endometriosis.

The specimen of colon contained a rather firm bulging tumor mass, 2.5 cm in length, which on microscopic studies revealed endometrial glands with absence of stroma. The mucosal lining of the colonic tumor was slightly atrophic.

Comment. It is interesting that this postmenopausal patient, with one remaining ovary appearing grossly atrophic, developed significant endometriosis. This is extremely rare. Despite this fact, the correct diagnosis was entertained preoperatively as a result of the characteristic roentgenographic picture. The surgeon added to the preoperative impression by noting that the lesion, in his

experience, felt softer than a carcinoma of the colon. This latter observation is in agreement with studies showing that plaques of endometriosis become softer, edematous, and friable following ovarian suppression (25). Also, an extensive exploration was performed to help rule out the possibility that the lesion represented a metastatic implant. Carcinomatous and endometrial implants involve mainly the serosa and muscularis with sparing of the mucosa, thus adding further difficulties to the preoperative diagnosis.

Case 4

A 32 year old nulliparous female, four years married, was admitted to The Mount Sinai Hospital with a history of rectal bleeding, diffuse abdominal pain, and recent weight loss. Menstrual history was unremarkable. Work-up included a negative sigmoidoscope. Barium enema revealed a polypoid defect in the descending colon. The hemoglobin on admission was 12.5 Gm per cent.

At laparotomy, what appeared to be a polyp was felt in the sigmoid. This was described as a hard nodule felt through the wall of the descending colon. An obstructive resection was performed. The specimen contained endometriosis of the colon. There was a nodular reddened area on the serosa and scarring of the muscularis. The mucosa was pale and edematous. No polyps were found nor were diverticula noted.

Comment. This case shows that endometriosis may not only be confused with carcinoma but also with polypoid lesions of the colon, as noted in other reports (7, 16).

Case 5

A forty-one year old para two gravida two housewife was admitted to The Mount Sinai Hospital with a recent history of dysmenorrhea and bright rectal bleeding several days preceding each menstrual period. Increasing constipation also had been a problem. On vaginal examination, the uterus was anteverted and of normal size and shape, but decreased mobility was noted. There was a nodularity of the rectovaginal septum. X-ray examination revealed the presence of a large tumor of the rectosigmoid resulting in a partial obstruction. At sigmoidoscopy, the mucosa lining the tumor was intact and appeared normal.

The diagnosis of endometriosis of the rectosigmoid and pelvis was confirmed at operation. The patient underwent a panhysterectomy and segmental resection of the bowel. Microscopic examination revealed endometrial tissue located in the submucosa and muscularis. The latter was also somewhat hypertrophied. The mucosa overlying the tumor was not ulcerated but appeared granular.

Comment. This patient demonstrates the unusual situation in which there was cyclic symptomatology thereby helping to make the correct diagnosis preoperatively.

Case 6

A 37 year old single business woman was admitted to The Mount Sinai Hospital complaining of cyclic rectal bleeding over a six month period. Prior to this period the patient had complained only of infrequent episodes of diarrhea. Regular menstrual periods were accompanied by mild episodes of dysmenorrhea.

About six months prior to admission the patient noted the onset of diarrhea and rectal bleeding lasting for two to three days about the time of her menses. Following this initial episode an upper gastrointestinal series and barium enema were unrevealing.

Several weeks prior to admission the rectal bleeding although scant was noted almost every day, with an increase in rectal bleeding associated with the menses. She was subse-

quently admitted with a repeat barium enema showing a polypoid defect in the lower sigmoid. Physical examination was unremarkable except for a slightly enlarged fibroid uterus.

At laparotomy a 3 cm tumorous mass, the center of which showed serosal puckering and hyperemia, was noted in lower sigmoid. Several other small whitish areas were present in the pelvis. A frozen section of one such area revealed fibrosis. In view of the possibility that the lesion represented a carcinoma an anterior resection with a supplementary tube cecostomy was performed.

Gross examination of the specimen revealed an intact mucosa. A cherry sized elevation 3 cm in diameter projected into the lumen of the bowel. There was focal thickening of the colonic wall adjacent to the mass. One small focus in and around the zone of serosal puckering showed multiple punctate hemorrhagic areas.

Microscopically the diagnosis of endometriosis of the sigmoid was confirmed. No evidence of malignancy was present.

Case 7

A fifty year old psoriatic menopausal mother was admitted to The Mount Sinai Hospital with an acute onset of rectal bleeding, frequent rabbit-like stools and suprapubic cramps. There was no history of diarrhea, tenesmus, chills and fever, or recent weight loss. Examination revealed a mass occupying the cul-de-sac and attached to the rectum. The uterus was freely movable and of normal size. At sigmoidoscopy fresh blood and a purulent discharge appeared to be coming from above a narrowed area of bowel. Stools were negative for ova and parasites. Barium enema failed to show any evidence of an organic lesion, although moderate spasm of the sigmoid was noted. An exploratory laparotomy was performed. An area on the anterior wall was indurated with scarring of the serosal surface. A similar lesion was seen on the sigmoid. A gynecologist thought the lesions on gross appearance resembled amebic ulcers or endometriosis of the rectosigmoid.

Gradual intermittent signs of colonic obstruction appeared. Although sigmoid biopsy revealed acute and chronic ulceration, localized radiotherapy was given in view of the diagnosis of endometriosis. No improvement was noted. A second laparotomy was undertaken and a temporary colostomy was performed for ulcerative colitis.

On the eleventh postoperative day the patient died as a result of a generalized peritonitis from a perforation of the bowel distal to the colostomy site. Autopsy revealed endometriosis of the rectosigmoid associated with ulcerative colitis.

Comment. This patient exemplifies the many diagnostic pitfalls in differentiating inflammatory and infectious diseases from endometriosis.

SUMMARY

A. Endometrioma of the bowel may mimic inflammatory or neoplastic diseases of the large bowel. Ways of differentiating these diseases are discussed.

B. Six cases of colonic lesions secondary to endometriosis causing large bowel obstruction are recorded.

C. It is suggested that endometrial lesions, as a factor in large bowel obstruction in women fifty years of age and under, appear more frequently than usually considered clinically.

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Clinico-Pathological Conference

JAUNDICE AND PAROTITIS WITH UNUSUAL TISSUE REACTION

Edited by

FENTON SCHAFFNER, M.D.

A 44 year old white married accountant was admitted to The Mount Sinai Hospital complaining of chills, fever and cough of ten days duration. He also noted undue tiredness, anorexia, generalized pruritus and urine somewhat darker than normal. He had been nauseated a few times but had not vomited. He had no pain. On the day before admission his sclerae were seen to be icteric. His cough was not severe and the height of his temperature was not recorded. A month prior to the onset of his present illness, the patient had bilateral shoulder pain for which he was given 15 tablets of phenylbutazone. At the beginning of the illness he was given Mysteelin® for a few days and this seemed to cause soreness of his palate. He had no significant illness in the past. He had an appendectomy and right inguinal herniorrhaphy in childhood.

On examination he was an obese, perspiring man with a temperature of 100°, pulse of 100 min. and blood pressure of 110/65. The sclerae were icteric, the palate and uvula were reddened with some areas thought to be moniliasis. Submandibular, cervical, axillary and inguinal lymph nodes were felt. The neck, heart and lungs were normal. The liver edge was felt one fingerbreadth below the right costal margin and was not very tender. The spleen was felt about three fingerbreadths below the costal margin and was firm and tender. No other organs were palpated. The genitalia were normal. Rectal examination was normal and the stools were pale but not acholic. The lower extremities had a finely papular erythematous rash.

During the first week in the hospital, the urine specific gravity varied between 1.020 and 1.037, urinary albumin between 0 and 2+, urinary bile between 0 and a trace, and urinary urobilinogen between 1:40 and 1:80 with one value of 1:640. Occasional red cells, white cells and granular casts were seen in most specimens. Hemoglobin was 15.2 Gm% and white count 16,600/mm³ with 27% segmented forms, 44% band forms, 22% lymphocytes, and 5% atypical lymphocytes. In six days these changed to hemoglobin 12.2 Gm%, white count 10,000/mm³ with 18% segmented forms, 27% band forms, 53% lymphocytes and 2% monocytes with slight toxic granulations noted. Reticulocyte count was 2.8% and increased to 3.5%. Sedimentation rate was 76 mm/hr. Platelets were normal. Coombs test and lupus preparations were negative. The bone marrow showed plasmacytosis without lymphocytosis or abnormal cells. Aspiration of an axillary lymph node revealed reticulum cell hyperplasia but no abnormal cells. BUN was 18 mg%, blood sugar 81 mg%, bilirubin 1.9 mg% with 1.0 mg% conjugated (this dropped to 0.8 mg% with 0.3 mg% conjugated after five days), thymol turbidity 3.6 units, cephalin flocculation 2+, albumin 3.5 Gm%, globulin 3.2 Gm%, alkaline phosphatase 18.6 King-Armstrong units (this rose to 21.7

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KAU after five days), glutamic oxalacetic transaminase 61 units, calcium 9.2 mg%, phosphorus 4.6 mg% and amylase 29 units, all of the last four tests being run on the fifth hospital day. Electrophoresis showed a diffuse increase in gamma globulin. Heterophile agglutination was 1:14. Chest x-ray showed some poorly defined mottling at the right base medially but was otherwise normal. An intravenous cholangiogram was attempted but no visualization was obtained although no stones were seen in the right upper quadrant. An electrocardiogram was normal.

The patient was treated symptomatically. By the third hospital day severe parotitis was present. On the next day he experienced some itching after intravenous Cholografin[®]. On the fifth hospital day the liver and spleen were thought to be somewhat smaller. Two days later his temperature rose to 102.8° after being about 100° during preceding week. Blood culture was negative. A hematologic consultant suggested that the patient had a chronic inflammatory disease with a hemolytic state, lymphocytosis and hyperglobulinemia such as would be caused by brucellosis or sarcoidosis rather than lymphoma. On the eighth hospital day the parotid swelling diminished somewhat, the lymphadenopathy was the same, the liver was slightly smaller and less tender, and the spleen was the same. A slight amount of ascites was detected. The temperature spike of the previous day had receded to 101°, and by the tenth hospital day temperature was normal. On the eleventh hospital day, beginning early in the morning, the patient began to complain of severe polyuria and polydipsia. He became agitated, weak, short of breath and stated he had pain and difficulty in swallowing. He was found to be afebrile but extremely tachypneic. Blood pressure was 120/78 and pulse was 110/min. Air exchange was good and all the organs previously noted to be enlarged, *i.e.* liver, spleen, parotids and lymph nodes had decreased in size. No meningeal signs were present but some retraction of the head was seen with weakness of the flexor muscles of the neck. Bilateral facial weakness was even more conspicuous. Speech was slurred and dysarthric. Pupils and fundi were normal. All the deep tendon reflexes were absent although no Babinski sign was present.

At this time the urine contained 1+ albumin, 4+ sugar, 4+ acetone, a trace of bile, 1:40 urobilinogen and a few red and white cells. Hemoglobin was 12.2 Gm%, white count was 35,300 with 20% segmented cells, 59% band forms, 12% lymphocytes, 1% monocytes, 4% atypical cells, 1% promyelocytes, 2% myelocytes and 1% metamyelocytes. BUN was 61 mg% and blood sugar 654 mg%. Heterophile antibodies were still 1:14. Coxsackie and mumps complement fixation were both greater than 1:64 and APC virus was negative. Serum sodium was 126 mEq/l, potassium 6.9 mEq/l, chlorides 95 mEq/l and CO₂ 18.5 mEq/l. Spinal fluid pressure and dynamics were normal. Cell count was 16 crenated red cells and 12 white cells/mm³ with 10 lymphocytes and 2 leukocytes. Bedside chest film was normal.

He was now given oxygen (and later placed in a respirator), insulin, fluids, antibiotics, intravenous hydrocortisone, and Levophed[®] (when his blood pressure dropped to zero later the same day). The patient became stuporous and remained

so although his urine became free of sugar and acetone. His temperature rose to 104° and he expired the next day after an illness of three weeks and twelve days in the hospital.

*Dr. Solomon Silver**: This is the story of a 44 year old obese man who, about a month before he came to us, took 15 butazolidin® tablets for some nondescript pain in his shoulders and then shortly thereafter developed malaise, a little fever, generalized body aches, nausea, some dark urine, and he became icteric.

This is a fairly good story for hepatitis. A man with a nonspecific prodrome who gets icteric almost always has hepatitis, probably viral. He took a drug of known but not very great hepatotoxicity, namely, butazolidin, but there had been an interval of several weeks between the administration of the butazolidin and the appearance of the hepatic symptoms so that a causal relation is unlikely.

He was studied by the clinical group and at first sight there was no reason to suspect that a hepatitis was not the most reasonable assumption. Apparently he was not particularly sick. He had mild fever and evidences of hepatic cell injury as manifested by slight changes in the cephalin flocculation, an increase in the serum globulin fraction, mild icterus with urobilinuria, all of which was not at all inconsistent with a man in the early stages of hepatitis. He had a large liver and spleen and some enlarged lymph nodes. He had a mild erythematous lesion and he also had reddened areas in his mouth which, by a stretch of the imagination, could be put in the herpangina group. He had painful vesicles with some type of white membrane over these vesicles and as far as I can gather from the protocol, nobody seemed to be too disturbed about the nature of his illness or its severity. On about the third day he developed parotitis. I assume that he had enlarged parotids that probably were tender. It is difficult from the protocol to decide whether this was a suppurative or a nonsuppurative parotitis but the chances are it was nonsuppurative from the description.

There are other slightly unusual things in this story. He had a rather marked leukocytosis, particularly for a viral disease, with a shift to the left. He also had up to 31½ per cent reticulocytes—a rather unusual finding in an infection of this type, which suggests that some type of hemolytic process was occurring. It was not a severe hemolytic process because he still had 15 Gm of hemoglobin. This subsequently went down to 12 Gm so whatever hemolytic process was going on was not hyperacute.

Part of the urobilinuria may be explained by the hemolysis but he apparently had enough liver disease to explain it, particularly in the presence of bile in the urine, because in pure hemolytic icterus little or no bile appears in the urine.

Since he did not seem sick enough, at least to me, to get the suppurative parotitis that develops in prolonged debilitating illness, we must consider the possibility that this parotitis is specific. In other words, this may be a viral parotitis related to mumps. This was now the third day of his illness and as far as I can reconstruct the protocol, not too much is going on to cause any great concern.

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They did an intravenous cholangiogram and it was reported as a failure to visualize. This may have to be modified a little bit because Dr. Khilnani tells me that by reviewing the plates he can see the gallbladder and the common duct. This had disturbed me a little bit because it was difficult for me to visualize why a patient with relatively mild hepatocellular damage should completely fail to visualize with an intravenous cholangiogram. A fairly complete obstruction or severe hepatitis is necessary to cause nonvisualization.

He went along still not terribly sick as far as I can gather from the protocol although leukocytosis with the marked shift to the left persisted. Then, on the eleventh day in the hospital or one day before his death, a very bizarre, sudden, dramatic clinical episode occurred.

This man suddenly became hyperacutely ill. He showed symptoms of central nervous system disease of a bulbar type, as manifested by dysarthria, difficulty in swallowing, respiratory embarrassment to the point where the aid of a respirator was finally invoked, bilateral facial weakness, a rather acute encephalopathy, mostly limited to the base of the brain, with some agitation which would indicate some cortical injury at the same time.

As disturbing as this is, we suddenly are also faced by a man with a hyperacute diabetic syndrome. He came into the hospital with relatively mild liver disease and a blood sugar of 81 mg per cent and on the eleventh day he had a blood sugar of 654 mg per cent with 4+ ketosis, electrolyte depletion, hypochloremia, and hyperkalemia. He rapidly deteriorated and died in 24 hours although the diabetic syndrome seems to have been corrected by insulin because at his death or shortly before his death he was acetone-free.

Somewhere toward the end of his disease there is a note that he had a positive complement fixation test both for Cocksackie and for mumps in concentrations of greater than 1:64. Why he should have positive complement fixation to two unrelated viruses is a little difficult for me to understand. For a Cocksackie infection the prodrome would fit: the exanthem, the herpangina, the fever, even the blood picture with bone marrow plasmacytosis and the atypical lymphocytes.

He died in a state of shock in addition to the encephalopathy, and Cocksackie can cause a myocarditis. This is limited usually to infants and children but I assume it could affect the myocardium of an adult and certainly an encephalopathy can occur with the Cocksackie virus. We have to worry also about mumps to which he shows a positive complement fixation, and he has a parotitis as well as the complement fixation. The encephalopathy and perhaps the myocarditis in mumps, if anything, are more frequent than in Cocksackie infection.

The electrolyte disturbance which was terminal in this case could conceivably be an acute adrenal injury by the virus. Reports exist in the literature implicating both the virus of mumps and Cocksackie. The fact that he had a normal spinal fluid should not disturb us too much. These encephalopathies need not affect the spinal fluid. So, we must accept the twelve cells as normal. There is no note as to whether the protein was normal. An encephalitis without meningitis could explain these findings.

Now we must try to explain the hyperacute diabetic syndrome. There is a centrally conditioned diabetes dating back to Claude Bernard, and it is possible

that this peculiar diabetes may have been a manifestation of central nervous system injury. Of course it could have been acute pancreatic atrophy or necrosis although this seems a little unlikely. It seems to me that a patient who gets a mumps or a nonspecific pancreatitis to an extent sufficient to bring about such an acute diabetic syndrome would have abdominal symptoms that would dominate the entire clinical picture. He would have pain, shock, a classical picture of hemorrhagic pancreatitis, and there was nothing in the story to indicate that.

Progressive hepatic damage may be considered as a cause of the acute diabetes. There are isolated records of hyperglycemia with massive hepatic necrosis.

I considered sarcoid because this man had some liver disease, some renal changes and some nervous system manifestations. Sarcoid always must be thought of in the presence of facial diplegia, but I think there is enough in the central nervous system to explain the facial diplegia on the basis of the lesion in the brain itself.

The peculiar hematological picture was initially a hemolytic reaction with leukocytosis, and toward the end a real leukemoid reaction with 35,000 white cells, a striking shift to the left, and immature white cells appearing in the peripheral blood. Leukemoid reactions occur in many infectious states particularly in tuberculosis and in certain cases of massive liver atrophy but it is quite unusual. I am at a loss to explain this leukemoid reaction. To my knowledge it is not a common finding in the viral diseases.

We must go back to the acute diabetic syndrome which could have originated in the pancreas on the basis of atrophy secondary to mumps or associated with hepatitis.

We have a most bizarre clinical picture and it is extremely difficult, at least for me, to pull together the evidences of what clinically I must say is a relatively mild hepatitis and this fulminating, explosive terminal event with an acute or hyperacute diabetic syndrome and encephalopathic manifestations. Some of the virus diseases can behave bizarrely. I had occasion to start looking at some of these things and I was amazed at the multiplicity of organ involvements in Cocksackie and in mumps infection. Almost no organ system in the body is necessarily spared from these generalized viral infections.

Dr. Schneierson said that he has changed the antigen and he used to have high values but not any more, so 1:64 against mumps means that the patient has had mumps or has been exposed to the mumps virus relatively recently.

He was less willing to commit himself about the significance of the 1:64 Cocksackie titer.

As I see it, the pathologist perhaps is also going to have difficulties because I do not think he is going to find massive liver atrophy, and the type of encephalopathy that I visualize, if it is present in this case, could also be associated with relatively minimal gross changes in the brain and would require certainly a histological study of the brain.

I think that the peculiar hematological response, the hemolytic component with a reticulocytosis and the final leukemoid reaction are just nonspecific and could occur with almost any infectious disease.

Dr. Hans Popper†: Dr. Levitt was the attending physician and worried very much about this patient.

Dr. Marvin Levitt‡: Our thinking actually was very similar to that of Dr. Silver and we kept telling the family that this was a virus infection. There was a very firm spleen but not that of hepatitis. As a matter of fact, when I first saw him I thought he had infectious mononucleosis, but his spleen was so firm and he had a few lymph nodes, that I also thought about an underlying blood dyscrasia, but I never could prove it.

He was scheduled for biopsy of a large lymph node in the axilla. Throughout the disease, I was worried about some underlying lymphomatous disease which we were trying to implicate in making him vulnerable to this virus.

Dr. Silver: As you know, lymphoma was one of the things that I considered and the hematologists found no evidence for it. Certainly I think we can exclude a true leukemia. Bone marrow studies were negative. Hodgkin's disease or lymphosarcoma are unlikely and one is still left with the diabetes to explain.

Dr. Levitt: We thought that the diabetes was caused by cerebral involvement affecting the brain stem because his vasomotor and respiratory centers collapsed the day before he developed severe diabetes.

Question: This generalized acute infectious process together with a picture that suggests infectious mononucleosis at times has been described in acute toxoplasmosis.

Dr. Silver: How an adult in New York would pick up an acute toxoplasmosis is unknown to me. Unless one had a puncture of the spleen, I do not know how to establish it. With a patient who dies within a week of an infection, I certainly cannot deny its existence but I think it is quite remote.

Question: How about miliary tuberculosis?

Dr. Silver: Whenever you get a leukemoid reaction you always think of a miliary tuberculosis. I have no way of making this diagnosis.

Question: Some people feel that a lot of cases that mimic infectious mononucleosis are due to *Listeria* infection. I wonder if you can tell us anything about that.

Dr. Silver: This again is a disseminated infection. Unless you have either bacteriologic or serologic evidence, you have to say "maybe". We have neither, unfortunately.

Question: Can you connect the central nervous system with the spleen and the lymph nodes with the diagnosis of reticuloendotheliosis, a disease more known to pediatricians than to physicians treating the adults? These patients, however, have diabetes insipidus and not diabetes mellitus.

Dr. Silver: I would say reticulosis like Letterer-Siwe disease is certainly possible. This is sort of a disseminated response of the reticulum and we have evidence of irritation of the reticulum. It does not fit into any well characterized reticuloses or lipoidoses in my opinion.

Question: How about cytomegalic bodies in the lung?

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Dr. Silber: If you will look at the protocol, you will see there is a description of a little infiltration in the right lung, but there is hardly enough to consider giant cell pneumonia.

Dr. Mansho T. Khilnani§: We had two examinations of the chest and the first one, as was pointed out, showed slight elevation of the right leaf of the diaphragm and a few lines which are nonspecific. The cholangiogram showed very faint visualization of the gallbladder and a very faint bile duct.

Dr. Popper: This was indeed a very difficult case. We made a quick and very sure diagnosis of acute leukemia. There was hepatosplenomegaly and this obviously was an acute leukemia. However, we felt that we should take no chances so cultures were taken of all sites and we found enterococci in the spleen but the heart valve cultures were negative.

Then we started with histology. We knew there were rashes on the skin and pieces were removed from the extremities. Circumscribed infiltration was found with a variety of lymphoid and histiocytic cells and proliferation of vessels, nothing specific. Dr. Zak, who knows skin pathology better than anybody around here, saw this slide and thought maybe one should think of reticuloendotheliosis.

The brain was grossly hyperemic, did not show any striking gross changes, and on microscopic examination a few unimpressive abnormalities were found. The meninges showed an increased cellularity with some edema particularly in the medullary portion. There was distinct perivascular infiltration by lymphoid and histiocytic elements and I think there is no difficulty in explaining some of the terminal clinical manifestations as a result of mild meningo-encephalitis.

With the possibilities of mumps, Coxsackie, and similar things in our mind, our interest was directed toward the salivary glands and the lingual tonsil. The tonsil itself was not changed and the mucous salivary gland was not altered grossly. But under the microscope we found inflammation with giant cells and interstitial infiltration. This was a very unusual histologic aberration but epithelial giant cells do not belong to mumps. Therefore, we have a seroadenitis.

The submaxillary glands appeared swollen, yellow, hardened, and with a rather severe inflammatory reaction, again with giant cells which appeared to be epithelial (Fig. 1). With the PAS stain we saw that the mucus appeared to be an irritant stimulating the giant cells which formed around the mucus. All kinds of bacterioscopic stains were used without any success. There were neither fungi nor inclusions in any of the organs.

The parotid gland was swollen and large. It was the site of a very severe inflammation which was not suppurative nor ascending through the duct in an emaciated person. This was primary inflammation involving the gland with lymphoid infiltration. Under the microscope we had no difficulty in seeing marked involvement of the ducts with rather irregular and extensive lymphoid and plasma cellular and also giant cell infiltration and proliferation of the epithelium. This was severe seroadenitis involving all the salivary glands, the serous as

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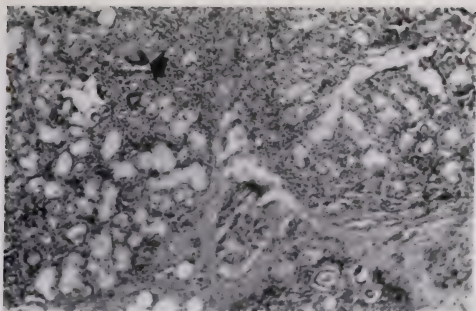


FIG. 1. Submaxillary gland showing severe inflammation and giant cell formation (arrow) (H & E $\times 63$).

well as the mucous ones. We saw irregular destruction of the acini surrounded by lymphocytes and partly reticular, partly inflammatory tissue.

We next looked at the pancreas because we wanted to know whether the salivary gland of the abdomen was involved. The pancreas was swollen, hard and distended, with fat necrosis. There were a few areas of fat necrosis. When we looked microscopically, we saw a diffuse, distinct pancreatitis, but nowhere were inclusion bodies noted (Fig. 2). In the acini small areas of fat necrosis developed which meant lipase must have escaped and led to the deposition of fatty acids seen in the form of bluish crystals. In areas of destruction of acini, giant cells formed around some irritant which appeared to have a mucoid character. The ducts were involved. Inflammation and transformation of the ductal epithelium were found favoring production of local obstruction. This was a fairly subacute type of pancreatitis, at least two or three weeks old, since it was associated with some fiber formation.

We have demonstrated involvement of all these groups of glands and we have to show you that diabetes may have been related to it. However, acute necrosis, probably very recent, of the island cells was also seen. The acute diabetes in this case was really pancreatogenic diabetes with destruction by round cells and only a few segmented leukocytes to a degree to which I have rarely seen. We saw scattered beta granules in only a few cells explaining the acute pancreatic diabetes which developed only in the last one or two days of life from destruction of the pancreatic islands.

Recently there were two papers making the point that the thyroid is involved in mumps. In Israel, a series of cases of acute thyroiditis were reported in two of which the virus was recovered, and in one case in England, it was demonstrated with what appeared to be a mumps virus producing subacute thyroiditis. The English patient had a high titer of thyroglobulin antibodies. That means antibodies were present as a result of virus destruction and release of thyroglobulin,

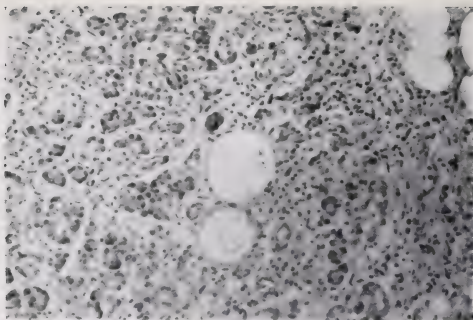


FIG. 2. Diffuse inflammatory infiltration of the pancreas with destruction of acini and areas of fat necrosis (H & E $\times 63$).

producing the immunologic reaction of thyroiditis. In our patient's thyroid we again found giant cell formation and destruction. This was a moderately sub-acute but still active thyroiditis (Fig. 3).

Actually, this patient had a very diffuse disease. All muscle tissue we examined contained giant cells and lymphoid and reticuloendothelial infiltration. The lungs grossly showed little. Microscopically the hilar lymph nodes were somewhat altered, with a slight increase of fibrous tissue. Focal fibrosis was present in the lung, but appeared old and was probably not sufficient to explain the respiratory changes. We saw some thickening around the alveoli and infiltration with giant cells.

The question of myocarditis was raised. We first looked at the valves and they were entirely normal. In the myocardium there were changes of myocarditis with lymphoid as well as giant cells (Fig. 4). It was a widespread lesion. The giant cells were arranged around PAS positive material which was broken down connective tissue. I think it was a hypersensitivity reaction almost resembling rheumatic fever but surely not representing it. The same was seen in the pericardium, with giant cells, infiltration and destruction.

The spleen was large, weighing 500 Gm. There were circumscribed, reddish and irregular foci and the architecture was accentuated but not altered. In the red pulp, quite significant reticuloendothelial proliferation was seen. There were a large number of plasmacytoid cells and some PAS positive extracellular material. We also found foam cells which was rather peculiar. It pointed to some tissue breakdown taking place, leading to fibrocytosis and formation of foamy material. A more exciting feature in the spleen was necrosis which was circumscribed with polymorphonuclear leukocytes and reticuloendothelial proliferation, again with some giant cells, probably stimulated by some tissue breakdown material which we thought we could demonstrate.

The lymph nodes showed a diffuse lymphadenopathy. They showed a normal

architecture in general. The medullary sinuses were not quite clear but under the microscope we saw a mixture of reticuloendothelial and lymphocytic cells with hyperplasia somewhat obscuring the architecture, and irritation of the lymph node. There were small foci of necrosis, again with polymorphonuclear leukocytes around them, and with tissue breakdown and digested material apparently attracting them.

The bone marrow was of interest in view of the question of the leukemoid reaction. Microscopically the architecture was quite intact. There was intensive megakaryocytosis and we saw really three types of cells: megakaryocytes, relatively many reticulum cells, and a large number of various eosinophils, but no leukemia.

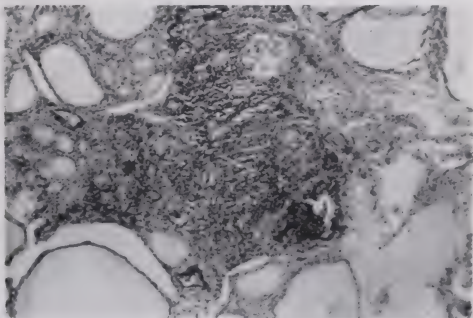


FIG. 3. Subacute interstitial infiltration of the thyroid gland with giant cells and plasma cells (H & E \times 63).

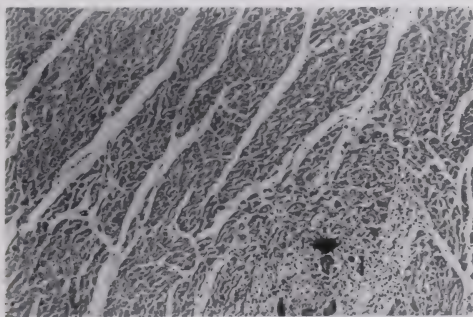


FIG. 4. Section of left ventricle showing focal myocarditis and the presence of giant cells (arrow) (H & E \times 63).

The liver, which obviously interested all of us, was rather large and weighed 2,600 Gm. The architecture was quite normal. Portal inflammatory reaction, central fat accumulation, and quite a lot of necrosis were present. This was probably a viral hepatitis but it was not epidemic viral hepatitis of the liver which probably accounted for the whole picture as shown to you. The portal inflammatory reaction was quite typical of epidemic hepatitis. However, there were some other features. In the centrilobular zone, there were changes in the fat. The fat droplets looked a little peculiar because they contained crystals. We saw fat crystals in many Kupffer cells. When we put them under the polarizing microscope, we saw the fat crystals quite distinctly. This may be an artefact as a result of fat somewhat changing in the fixative or else it could be fat from the pancreatic fat necrosis (1-3). The bluish crystals were deposited in fat droplets, the bluish crystals being fat necrosis. The same picture which we saw in the pancreas was also in the liver with digestion of the fat probably by lipase in the liver. It could have reached the liver in two ways: either by regurgitation through the common duct from the pancreatic duct, or by the hematogenous route. Tissue breakdown products with a lot of protein particularly around the fatty areas led to reactions and some of them were giant cell reactions (Fig. 5). First we saw an irritating mucus-producing reaction and in the liver we have lipase creating a reaction. I think the giant cells are taking up tissue breakdown products possibly as a result of pancreatic lipase being circulated through the body. Giant cells appeared in the most peculiar spots. For instance, in the stomach a group of giant cells were seen (Fig. 6) whereas in the intestinal muscularis the same infiltration was present that was in the muscular tissue elsewhere.

The kidneys were not significantly altered grossly but a diffuse, rather severe interstitial nephritis was found microscopically quite extensively involving the interstitial tissue of the cortex and the medulla (Fig. 7). It was associated with breakdown of tubules so I could imagine that in part this led to the azotemia. Again giant cells with the same type of exudative pattern were seen. The kidney

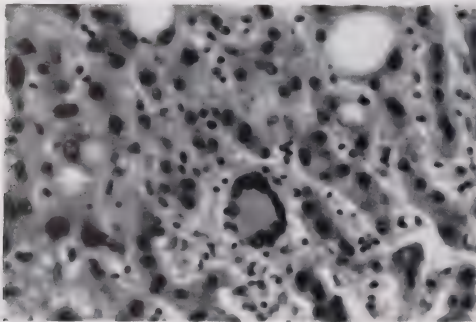


FIG. 5. Giant cells in inflammatory exudate in portal tract of liver (H & E $\times 240$).

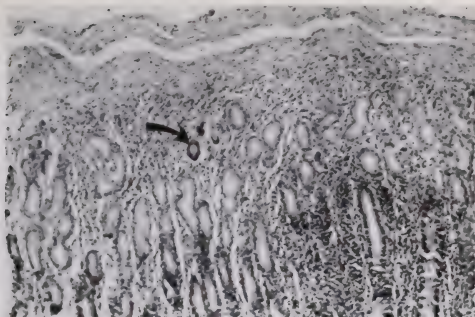


FIG. 6. Isolated giant cells in the mucosa of the stomach (arrow) (H & E $\times 63$).

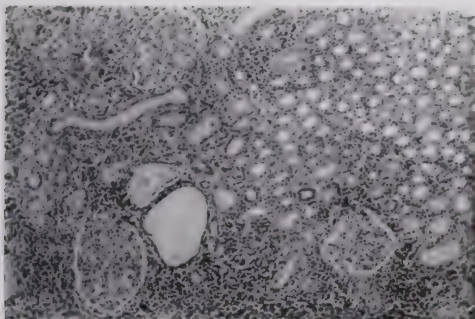


FIG. 7. Extensive interstitial infiltration of the kidney with mononuclear cells (H & E $\times 63$).

contained a large amount of two types of fat, fat in the fine droplets in the cells and in the distal convoluted tubules, the same type of crystals that we had seen in the liver. These crystals were not oxalate.

Every organ I examined essentially showed this same type of reaction with the giant cells. In the testes we found circumscribed atrophy with inflammation and this inflammation was fairly acute (Fig. 8). There were some giant cells again present and also some fibrosis.

Obviously it was a bewildering case anatomically. There is much in the picture that should suggest mumps. We have the selective distribution of organs in which mumps may be present, namely, salivary gland, thyroid, testes, heart and pancreas. It was a little more than we usually see in mumps.

We sent the case around to a variety of people who are known to be experts

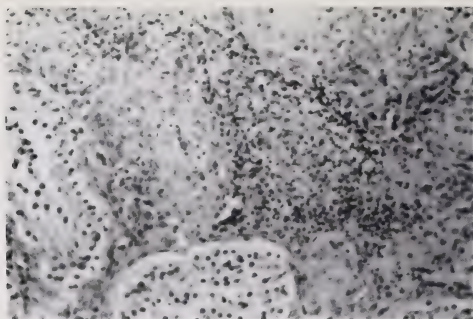


FIG. 8. Inflammatory fossa in testis with lymphoid cells (H & E $\times 120$).

in the infectious diseases and we got negative results. We were told that mumps produces giant cells in tissue culture but never in the human body (4, 5). Nevertheless, I must assume that it was mumps. I believe that we are dealing with mumps of probably three weeks duration or maybe older. I have heard that mumps may, under certain circumstances, be a much more prolonged disease. We had parenchymal necrosis which is known to be associated with some local lymphocytic and plasma cell proliferation. Local lymphocytic and plasma cell proliferation and atypical lymphocytosis was present in the salivary glands with delayed swelling, in the pancreas with the terminal islet necrosis producing diabetes, and also in the myocardium and thyroid. I think that this is probably a fairly unique case and I want to present it to you not as a diagnosis but as the way we tried to reason out a difficult situation. I think that there are secondary effects suggested. These are the tremendous endothelial and giant cell reactions and the hypergammaglobulinemia. There is indeed the possibility that under the effect of mumps an immune reaction may have been set up which accounts for these. This has been shown in the case of mumps thyroiditis (6-8). I would assume that in the myocardium, in the muscles, in the salivary glands, in the thyroid, in the gastrointestinal tract, in the liver, in the bone marrow, and in a variety of organs, tissue breakdown products lead to a secondary and possibly immunologic tissue reaction which is characterized by giant cell formation. There is a second hypothetical mechanism which is that circulating lipase and trypsin released from the sustained pancreatitis and seroadenitis led to the changes. I suspect that in the kidney something of this nature took place and I would assume that the splenic and lymph node necrosis is the result of a circulating material leading to digestions. I hope you will forgive me for presenting a case which remains hypothetical and I was fully aware that we would not have a definitive answer. This is a case in which we saw a very unusual tissue reaction, most probably belonging to mumps, which was modified by giant cell reactions

some of which may have been chemical in nature resulting from enzymes from the pancreas and salivary glands and others which may be in the more mysterious realm of an immunologic reaction.

Dr. Silver: I had planned to speak about the thyroid because the protocol mentions a tender neck and a rapid sedimentation rate. These should always alert one to the diagnosis of thyroiditis. I am familiar with the relationship of mumps to some types of subacute thyroiditis, and in a school that had an epidemic of mumps quite a few of the nursing sisters came down with thyroiditis, so this is another item which may tie in with mumps.

But we still have certain problems as clinicians. We think of pancreatitis especially in a patient who develops acute diabetes, but pancreatitis to us is a clinical disease associated most commonly with a catastrophic abdominal picture. This man had none of it. The lesions in the pancreas here are of long duration. The symptoms of the pancreatic deficiency, certainly the island cell deficiency, are of 24 hours duration, so that it does not seem to make sense from a purely clinical point of view.

Dr. Popper: There was no massive necrosis. That may be the key.

Dr. Silver: We had the 1:64 mumps titer and also a 1:64 Coxsackie titer. These are serologically unrelated organisms.

Dr. Popper: It was pointed out that there may be an amnestic reaction to Coxsackie but no amnestic reaction to mumps.

Dr. Silver: In an international journal of virology published in Prague which has an English edition, I found a good deal of information on the systemic lesions in mumps. This apparently has created a great deal of interest and these lesions in the myocardium, pancreas, adrenal and certainly in the thyroid and the muscles should excite our interest and should alert us to the fact that what we ordinarily consider an incidental, mild pediatric affliction sometimes can result in extensive disseminated disease even in the adult.

Question: Were the adrenals involved?

Dr. Popper: They were depleted of lipids but otherwise normal.

Question: Why was the amylase only 29 units?

Dr. Popper: There is the question of protracted pancreatitis. We know that in the very slowly progressing pancreatitis we do not expect elevations.

Dr. Silver: Unless you get multiple amylase determinations, you cannot evaluate a single result.

Final diagnosis:

A. MUMPS INVOLVING THE SALIVARY GLANDS, THYROID, MYOCARDIUM, PANCREAS AND TESTES WITH UNUSUAL GIANT CELL REACTION. B. FAT NECROSIS OF KIDNEY, SPLEEN, LIVER AND LYMPH NODES (FROM MUMPS PANCREATITIS?).

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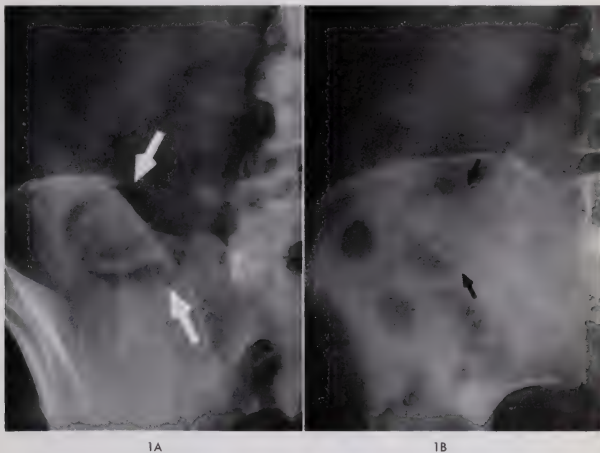
Radiological Notes

BERNARD S. WOLF, M.D.

New York, N. Y.

CASE NO. 120

This was the first admission of a 53 year old female with the chief complaint of pain in the abdomen. Pain started in the right lower quadrant four days prior to admission and was followed about five hours later by two episodes of vomiting. The patient denied chills or fever. About forty years previously she had been treated for 14 days with ice bags to the right lower quadrant because of acute appendicitis. She noted that for several years she had experienced mild transitory pain in the same area.



Case 120, Fig. 1A. Prone. At the level of the right iliac crest, a tortuous ribbon-like collection (arrows) of gas is seen which has the configuration of the appendix.

Case 120, Fig. 1B. Supine, left side elevated. The tortuous ribbon-like appearance is maintained. The gas filled appendix extends between the arrows. The origin of the appendix (lower arrow) joins a gas filled haustrum in a funnel-shaped fashion.

Examination on admission showed exquisite tenderness in the right lower quadrant with rebound and referred rebound tenderness. In this area, a poorly defined mass was palpated. Temperature was 101°.

The original clinical impression included the possibility of a pelvic infection. Films of the abdomen showed a fixed coiled gas-filled appendix with fluid in the

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Case 120, Fig. 1C. Lateral decubitus view with right side up shows fixation of the gas filled appendix which does not change its location or configuration. In this position a short fluid level (arrow on reader's left) is seen near the origin of the appendix. The tip of the appendix shows a transverse cut-off (arrow on right) which probably represents inspissated or semi-solid content.

bowel near its origin (Figs. 1A, 1B, 1C). The diagnosis of acute gangrenous retrocecal nonperforated appendicitis was made. At laparotomy, a gangrenous appendix was found behind the cecum with adherent omentum. There was no perforation. Routine appendectomy was performed. The postoperative course was uneventful. Incidentally, roentgenogram of the removed appendix showed no gas in the wall of the appendix or adherent soft tissues.

The presence of gas in the appendix may be seen in the absence of acute inflammation. A retrocecal appendix directed-upwards traps gas which may persist. In such cases the wall of the appendix is smooth and no fluid or irregular densities are seen within it. The presence of dilatation of the appendix and fluid in its lumen are said to indicate gangrenous nonperforated appendicitis.* A more reliable sign of gangrene, if it can be recognized, would be gas within the wall of the appendix.

Case Report: ACUTE GANGRENOUS APPENDICITIS GAS IN THE APPENDIX;

CASE NO. 121

SUBMITTED BY PAUL WERMER, M.D., AND STUART I. GURMAN, M.D.

The patient is a 70 year old white male seen originally in 1957 for hepatosplenomegaly and generalized lymphadenopathy of recent onset. Biopsy of a supraclavicular node was reported as "giant follicular lymphoblastoma" but containing elements of small cell lymphosarcoma. No specific treatment was instituted at that time. About two years later, however, the patient was anemic

* Fisher, M. S.: A Roentgen Sign of Gangrenous Appendicitis. *Am. J. Roentgenol.*, 81: 637, 1959.

with marked enlargement of the spleen which extended below the umbilicus and into the right side of the abdomen. The liver margin was felt four fingerbreadths below the costal margin. Enlarged nodes were palpable in the axillae and the inguinal regions. Radiotherapy with Co^{60} was given to the left side of the abdomen as far down as the level of the crest of the ilium. The right side of the abdomen was treated with a field which also extended below the iliac crest level. A total of 1,000 roentgens was given to each side. The patient developed no untoward hematological reaction and the liver and spleen decreased in size.

The patient was in generally good health for about seven or eight months but then developed mild diarrhea with bright red blood in the stools. Barium enema (Figs. 1A, B and C) showed marked coarsening of the mucosal folds in the rectum and distal sigmoid with innumerable nodular protrusions into the lumen.



Case 121, Fig. 1A. Barium enema shows marked irregular coarsening of the "mucosal folds" in the rectum and distal sigmoid without any limitation in distensibility. In fact, the distal sigmoid is more distensible than normally seen.



Case 121, Fig. 1B. Spot film of the filled rectum and sigmoid shows totally bizarre contours with, in places, fingerprint indentations into the barium column.

The bowel was not limited in distensibility, there was no irritability or definite evidence of ulceration. These changes stopped rather abruptly in the sigmoid and the remainder of the colon except for the cecal region was normal. The cecum showed changes similar to those seen in the rectum. The roentgen findings were interpreted as the result of the diffuse type of lymphosarcoma of the colon in which the submucosa and mucosa are uniformly infiltrated with tumor tissue. In this variety, discrete masses are not seen. It seemed likely that the sparing of the colon between the cecum and the distal sigmoid was the result of previous radiotherapy to the abdomen which included the undiseased portions of the colon in the treatment fields.

A course of radiotherapy was then given to the rectosigmoid area. Barium enema (Fig. 2) after 2,000 roentgens showed no abnormality in the rectum or sigmoid. This type of lymphosarcoma is quite radiosensitive and does not require



Case 121, Fig. 1C. After evacuation, the wide lumen of the rectum and rectosigmoid is filled with innumerable nodular or sessile pseudopolypoid protrusions which in places become confluent. The transition to normal sigmoid appears to be quite abrupt.

so-called "cancericidal" doses. The ultimate prognosis, of course, is quite poor because of the spread of disease elsewhere in the body.

Case Report: DIFFUSE TYPE OF LYMPHOSARCOMA OF THE COLON; "SKIP" AREA DUE TO PREVIOUS RADIOTHERAPY.

CASE NO. 122

SUBMITTED BY CLAUDE BLOCH, M.D.

This was the first admission of a 62 year old Mexican male with the chief complaint of hoarseness of two months duration. There was no history of previous significant illnesses. The patient denied local pain, dysphagia, hemoptysis, cough or fever. Examination on admission showed a well developed male in no acute distress. Positive findings were limited to the laryngeal region. On laryngoscopy, the valleculae and the pyriform sinuses, the epiglottis and the aryepiglottic folds were normal. Both vocal cords were restricted in motion; the maximum glottic chink was about 4 mm. On the anterior half of the right vocal cord, there was a granular polypoid soft tissue mass covered by smooth, pale pink



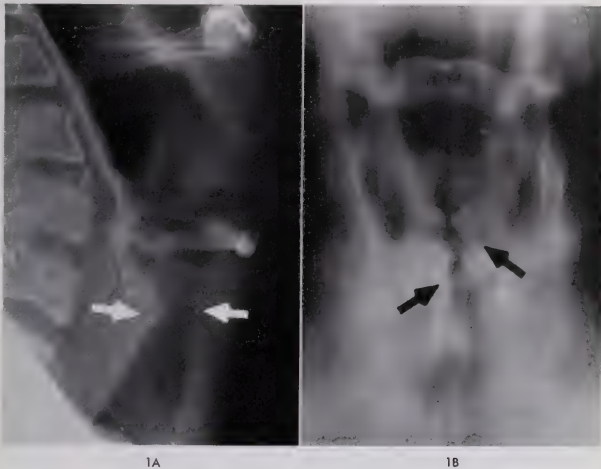
Case 121, Fig. 2. Barium enema after radiotherapy shows a normal appearance of the rectum and sigmoid.

mucosa. This mass extended to the anterior commissure and onto the under aspect of the anterior portion of the left vocal cord. It was evident also that the lesion extended inferiorly into the subglottic region for a distance of about 1.5 cm.

A lateral roentgenogram of the neck (Fig. 1A) showed a somewhat fusiform narrowing of the subglottic region extending downwards into the trachea a distance of about 2 cm. The narrowing was most marked posteriorly. Both margins of the trachea showed an irregular slightly scalloped surface. The supraglottic structures appeared normal although the ventricles and cords were not demonstrated. Anteroposterior laminagraphy (Fig. 1B) of the larynx revealed no abnormalities of the structures above the false cords. The false cords appeared to be asymmetrically enlarged to a moderate degree. The laryngeal ventricles were shallow and unequal in size. The vocal cords were distinctly thickened and merged inferiorly with marked circumferential thickening of

the subglottic tissues which extended distally in a somewhat irregular fashion for a distance of about 2 cm. The caliber of the subglottic airway was markedly reduced to a width of about 4 mm.

The roentgen findings appeared rather atypical for a neoplastic process in the sense that the maximum involvement appeared to be in the subglottic area involving the upper portion of the trachea and was circumferential in nature without the formation of a discrete mass or obvious ulceration. Extensive subglottic involvement in a patient of Mexican origin suggests the diagnosis of rhinoscleroma. While this is usually associated with involvement of the nasal passages and sinuses, this apparently was not true in the present instance. In this patient therefore, a more correct term is scleroma of the larynx. This diagnosis was confirmed by histological examination of tissue removed from the subglottic region which revealed granulomatous lesions characteristic of rhino-



Case 122, Fig. 1A. Lateral view of the neck shows symmetrical narrowing (arrows) of the subglottic region extending into the proximal portion of the trachea, most marked posteriorly. The margins of the trachea in the involved portion are irregular and slightly serrated.

Case 122, Fig. 1B. Anteroposterior laminagram of the larynx shows moderate increase in size of both false cords. The right ventricle is rather shallow. The left is almost completely obscured (upper arrow). There is marked thickening in the region of both true vocal cords. This thickening extends downwards in circumferential fashion for a distance of about 2 cm (lower arrow) narrowing the airway in a somewhat fusiform fashion. The aryepiglottic folds and the pyriform sinuses appear to be free of disease.

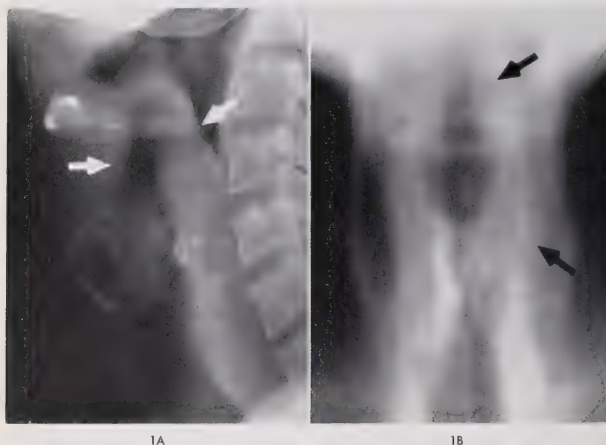
scleroma. Cultures demonstrated the presence of *B. Friedlander* (Type A) known as the Frich bacillus. This organism was demonstrated to be sensitive to streptomycin and the broad spectrum antibiotics and the patient was started on therapy of this type.

Case Report: RHINOSCLEROMA OF THE LARYNX.

CASE NO. 123

SUBMITTED BY CLAUDE BLOCH, M.D.

This was the first admission of a 43 year old Puerto Rican male with the chief complaints of dysphagia for solid foods and of hoarseness of four weeks duration. He had noted low grade fever, a non-productive cough and a 15 pound weight loss. He denied night sweats and hemoptysis. Examination on admission showed a well developed male who appeared chronically ill. A soft movable, nontender, 2 cm lymph node was noted in the right submaxillary region just below the angle of the mandible, and small discrete nodes were felt along the anterior



Case 123, Fig. 1A. Lateral view of the neck shows marked thickening of the entire epiglottis (anterior arrow) including its tip as well as of the aryepiglottic folds (posterior arrow). The subglottic space is normal.

Case 123, Fig. 1B. Anteroposterior laminogram of the larynx reveals diffuse marked thickening of the side walls of the vestibule, somewhat more marked on the left (upper arrow). The left pyriform sinus (between arrows) is effaced. The false and true cords are irregularly enlarged and confluent, obliterating the ventricular cavities. The airway at the level of the cords is markedly reduced.

edge of the right sternomastoid muscle. No other positive findings except those seen on laryngoscopy were noted. Temperature was 100.5°. Blood count and urine analysis were within normal limits. On laryngoscopy, the epiglottis, the aryepiglottic folds and the arytenoid regions were markedly reddened and edematous. There was a deep ulceration on the right side of the epiglottis extending into the pyriform sinus. The false cord on this side was thickened although the vocal cord appeared to move normally.

Roentgen examination of the neck in the lateral projection (Fig. 1A) revealed huge thickening of the epiglottic tip and aryepiglottic folds as well as of the body of the epiglottis itself. The subglottic space appeared to be normal. Laminagrams in the anteroposterior projection (Fig. 1B) confirmed marked thickening of the aryepiglottic folds extending into the left pyriform sinus. Both the true and false cords appeared to be irregularly enlarged with effacement of the laryngeal ventricles. The laryngeal airway at the level of the glottis was markedly diminished. Comparison of tomograms taken in phonation and quiet breathing indicated that there was diminished motion of the true cords.

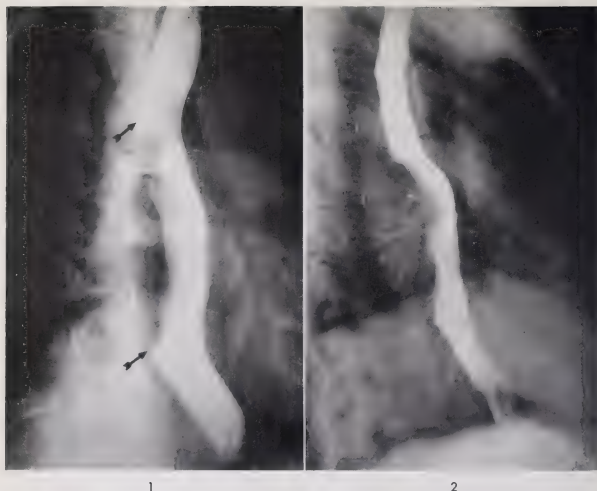
The rather diffuse and extensive nature of the infiltrating process with a fairly symmetrical distribution occurring in a relatively young patient is not typical of neoplastic involvement of the larynx but is suggestive of a chronic inflammatory process. Laryngoscopic and roentgen findings were consistent with the diagnosis of tuberculous laryngitis. While attention originally was focused on the larynx in this patient, a subsequent film of the chest revealed bilateral diffuse, coarse, slightly nodular infiltrations in the upper lobes of both lung fields without demonstrable cavitation. Biopsies of multiple sites in the larynx revealed granulomatous, noncaseating lesions of extensive nature. Acid-fast bacilli were found in the sections.

Case Report: TUBERCULOSIS OF THE LARYNX.

CASE NO. 124

This was the first admission of a 41 year old negro male with the chief complaint of dysphagia. Difficulty in "getting food into his stomach" began about three months prior to admission. Food stuck in the xyphoid region and then by repeated efforts he was able to force it further. Dysphagia varied from day to day. It was more common with firm or solid foods. There had been no weight loss. About 15 years prior to admission, the patient stated that a duodenal ulcer had been demonstrated by x-ray examination and that he had symptoms for about five years after this. When questioned, he stated that he often had bleeding from the nose. Examination on admission showed a well developed and well nourished male with no pertinent physical findings. Hemoglobin was 13.3 Gm, while blood count was 12,000 per cu mm with a normal differential count.

Barium meal examination (Fig. 1) showed no delay to the passage of barium through the esophagus. However, there was an eccentric, flat, markedly elongated, somewhat lobulated filling defect on the posterior and right wall of the esophagus extending from about the level of the carina distally for a distance of about 15 cm. There was no evidence of ulceration. The course of the lumen



Case 124, Fig. 1. Barium swallow shows no obstruction to the flow of barium through the esophagus. There is a flat eccentric filling defect on the posterolateral wall of the esophagus extending for a distance of about 15 cm beyond the carina (between arrows). Over this segment, the lumen is displaced forwards and towards the left. On other films, there was evident a soft tissue mass corresponding to the filling defect which indicated huge thickening of the wall or extrinsic growth of the tumor. The proximal margin of the filling defect is not sharply delineated but the distal margin is indicated by an abrupt angle (lower arrow). The surface of the tumor has a rather flat lobulated contour. There is no evidence of ulceration.

Case 124, Fig. 2. Barium swallow after operation shows findings similar to those seen preoperatively. The extent of the soft tissue mass is better seen and the limits of the tumor are outlined by clips placed around the periphery for purposes of localization during radiotherapy.

of the esophagus at the site of the tumor was displaced forwards and toward the left. There was also evidence of an elongated, soft tissue density extending posteriorly and towards the right, continuous with the filling defect intruding on the lumen of the esophagus. The roentgen features were obviously quite unusual and were not characteristic of a carcinoma of the esophagus. The impression gained was that a huge elongated intramural tumor was present, perhaps an enterogenous cyst, perhaps a myoma. On esophagoscopy, a rounded indentation on the lumen was seen posteriorly beginning at 31 cm from the upper incisor teeth and extending distally for about 6 cm. The mucosa was intact. The impression of the esophagoscopist was that of a myoma.

At thoracotomy, a huge markedly vascular mass was found in the wall of the esophagus extending as high as the region of the azygos vein which seemed to be replaced or enveloped by angiomatous tissue. It was considered that this lesion was inoperable because of its extent and intimate association with adjacent structures. Biopsy was reported as "cavernous hemangioma". Opaque clips were placed around the periphery of the mass to permit more precise radiotherapy (Fig. 2).

Hemangioma of the esophagus is an unusual variety of intramural tumor. Myomas, fibrolipomas and enterogenous cysts are more common. At the time of discovery, an esophageal hemangioma is usually extensive and as in a current case, operative intervention is fraught with considerable difficulty. If the diagnosis of hemangioma is suspected, azygography by injection of opaque material into the ribs should be utilized to confirm this diagnosis. This was not done in the present case because the correct diagnosis was not considered preoperatively.

Case Report: CAVERNOUS HEMANGIOMA OF THE ESOPHAGUS.

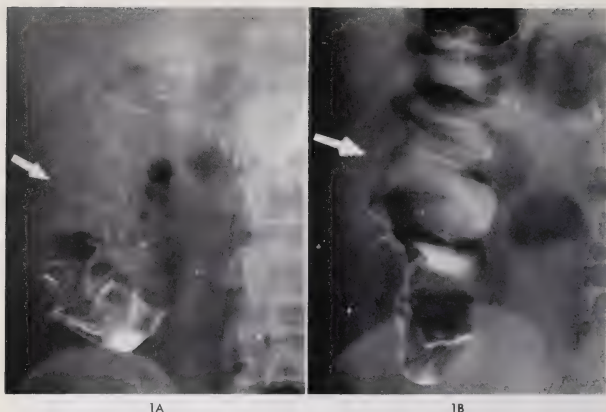
ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Bernard P. Robinson

CASE NO. 125

SUBMITTED BY BERNARD S. ARON, M.D.

A 58 year old Puerto Rican male was admitted with the chief complaints of generalized weakness, abdominal swelling and anorexia for eight months. There was a history of excessive alcoholic intake for about seven years. The patient, nine years before the current admission, had undergone a subtotal gastrectomy and gastroenterostomy for a bleeding duodenal ulcer. On that admission, there was no evidence of damaged liver function. Physical examination on this admission revealed a chronically ill, icteric male with obvious ascites. The liver margin was palpated three fingerbreadths below the right costal margin and the spleen about one fingerbreadth below the left. Spider nevi, palmer erythema and loss of body hair were clearly evident. Hemoglobin was 12.2 Gm per cent, total protein was 7.7 Gm per cent with 3 Gm per cent of albumin and 4.7 Gm per cent of globulin, alkaline phosphatase was 19.5 King Armstrong units, total bilirubin was 10 mg per cent and direct bilirubin was 7.6 mg per cent. The prothrombin time was markedly prolonged. Barium meal examination revealed the status post-subtotal gastrectomy with a well functioning gastrojejunostomy. In addition, there were obvious esophageal varices. Prior and subsequent to the barium meal examination, stool guaiac tests were positive. Two weeks after admission, the hemoglobin had fallen to 10.7 Gm per cent. Barium enema examination was done to search for an additional source of bleeding. A striking finding (Figs. 1A & 1B) was the marked thickening of the mucosal pattern of the cecum and ascending colon. Distensibility of these regions was limited; the contour of the distended bowel showed an irregular appearance suggesting a plastic type of thickening of the wall of the bowel. These findings did not have the appearance of an inflammatory process but were consistent with edema



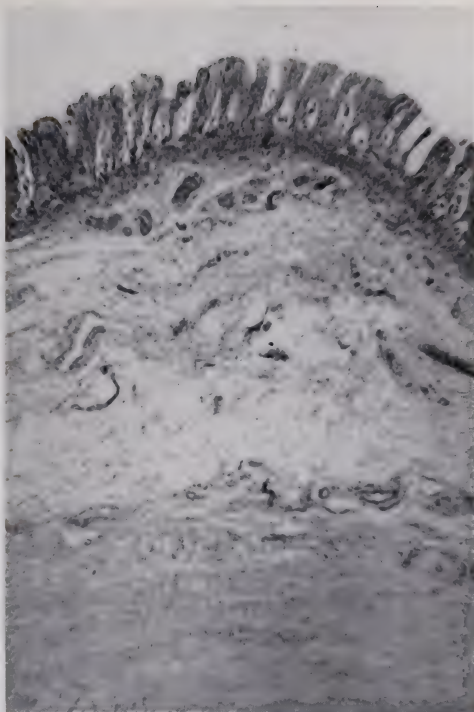
Case 125, Fig. 1A. Evacuation film taken after barium enema shows extreme coarsening of the mucosal pattern (arrow) of the cecum and ascending colon. The marked thickening of the bowel prevents complete collapse. There is no evidence of a discrete filling defect or of ulceration.

Case 125, Fig. 1B. Double contrast portion of the barium enema shows minimal decrease in distensibility of the cecum and ascending colon with a coarsely irregular contour (arrow) consistent with nonrigid thickening of the bowel wall.

and/or congestion presumably on the basis of portal hypertension. About four days after the barium enema, the patient developed a liver flap, progressive lethargy and massive hematemesis followed by bloody diarrhea. A Blakemore tube was passed and bleeding stopped with improvement in the condition of the patient. However, he pulled the tube out and expired shortly thereafter, on the nineteenth hospital day.

Post mortem examination showed severe ascites, six liters of fluid being present in the peritoneal cavity. Small bilateral pleural effusions were also present and there was a large amount of clotted blood throughout the gastrointestinal tract. The liver weighed 1,650 Gm and showed a hobnail appearance. The right side of the colon showed obvious severe submucosal edema which was also well demonstrated on histological examination (Fig. 2). Varices were present in the distal third of the esophagus and there were several erosions in the course of these varices as well as along the lesser curvature of the fundus of the stomach. Microscopic examination of the liver showed a pattern of post necrotic cirrhosis.

Submucosal edema of the colon without ulceration or inflammation in patients with cirrhosis of the liver coming to autopsy is not an infrequent finding at this institution. Such edema has, however, been rarely recognized *in vivo* by roentgen examination. If functional changes of a bizarre character are super-



Case 125, Fig. 2. Histological section of the right side of the colon shows marked thickening of the submucosa as a result of interstitial fluid. The mucosa and muscularis propria are intact.

imposed on the edema, differentiation from right sided ulcerative colitis may be difficult (1). The fact that the edema is most marked on the right side of the colon may be explained on the basis of the relatively sparse collateral communications of this region with the systemic venous drainage.

Case Report: SUBMUCOSAL EDEMA OF THE RIGHT SIDE OF THE COLON IN POST NECROTIC CIRRHOSIS.

REFERENCE

1. ARON, B. S.: Transitory Changes in the Colon Simulating Ulcerative Colitis in a Patient with Post Necrotic Cirrhosis. Radiological Notes, Case 96, J. Mt. Sinai Hosp., 26: 583, 1959.

Surgical Techniques

5. DIRECT-VISION CLOSURE OF INTERATRIAL SEPTAL DEFECTS

ISADORE KREEL, M.D., AND IVAN D. BARONOFSKY, M.D.

The development of effective pump-oxygenators allows the direct-vision closure of interatrial septal defects with precise anatomic repair, and an acceptably low mortality. The septum secundum defect is closed by direct suture.

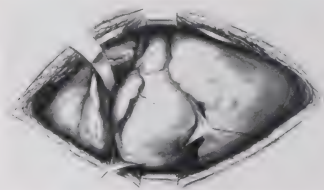


Fig. 1. The chest is opened by a bilateral transverse thoracotomy through the fourth intercostal spaces, and the heart exposed by a wide incision in the pericardium. A median sternotomy approach may also be used.

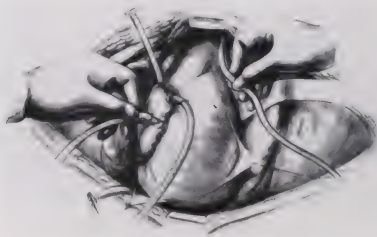


Fig. 2. The superior and inferior venae cavae are cannulated via the left atrial appendage, to obtain venous return to the pump-oxygenator. Arterialized blood is returned to the patient via a catheter inserted into the femoral artery (not shown).

If anomalous pulmonary veins co-exist, the interatrial septum is transposed to the right, allowing the pulmonary veins to drain normally into the left atrium. In ostium primum defects the cleft mitral and/or tricuspid valve are repaired

From the Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

The section on Surgical Techniques is one of a series prepared by the Department of Surgery. Some of the techniques described are original, others are of long-established application, some with modifications found useful here. The descriptions afford a concise review of techniques currently utilized at The Mount Sinai Hospital, New York.

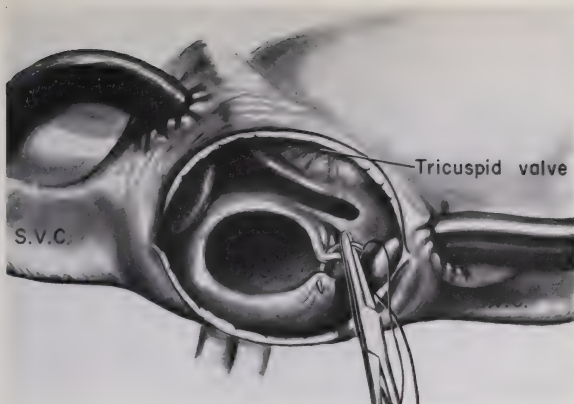


Fig. 3. After opening the right atrium widely, the septum secundum defect is closed by interrupted and continuous silk sutures.



Fig. 4. In low-lying secundum defects, an initial "three-cornered stitch" is taken in the lower aspect of the defect. One of the bites of tissue includes a small portion of the left atrium. When the suture is tied, the lower angle is effectively closed and the inferior vena cava correctly routed into the right atrium. The remainder of the defect is closed in the usual fashion.

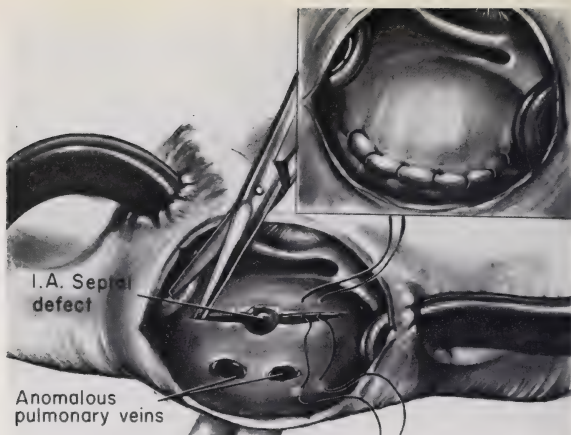


Fig. 5. Where anomalous pulmonary veins exist, the interatrial septal defect is enlarged and the anteromedial margin of this defect is sutured to the right atrial wall, posterior and lateral to the point of entry of the anomalous veins. The insert shows the defect completely closed. The anomalous veins now drain into the left atrium.

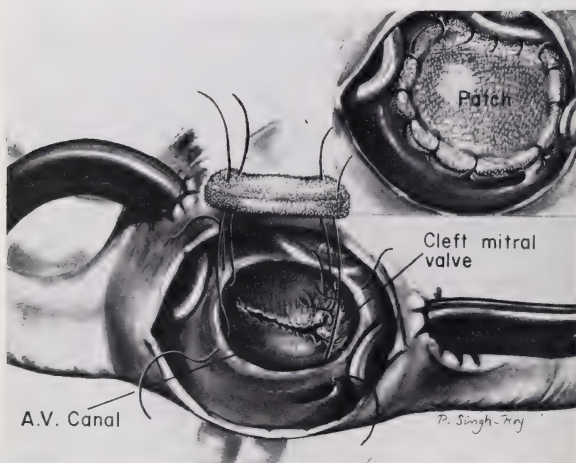


Fig. 6. In a septum primum defect, the cleft mitral valve is shown being repaired through the defect. A patch of Ivalon is then sutured down to the margins of the defect. The insert showed the patch in place. We have recently closed septum primum defects primarily, without the use of a patch.

by direct suture and the defect in the interatrial septum is closed with a patch of Ivalon.

The following diagrams demonstrate the techniques utilized at The Mount Sinai Hospital in a series of more than thirty interatrial septal defects.

ACKNOWLEDGMENT

Figures 3 through 6 appear through the courtesy of W. B. Saunders Co., publishers.

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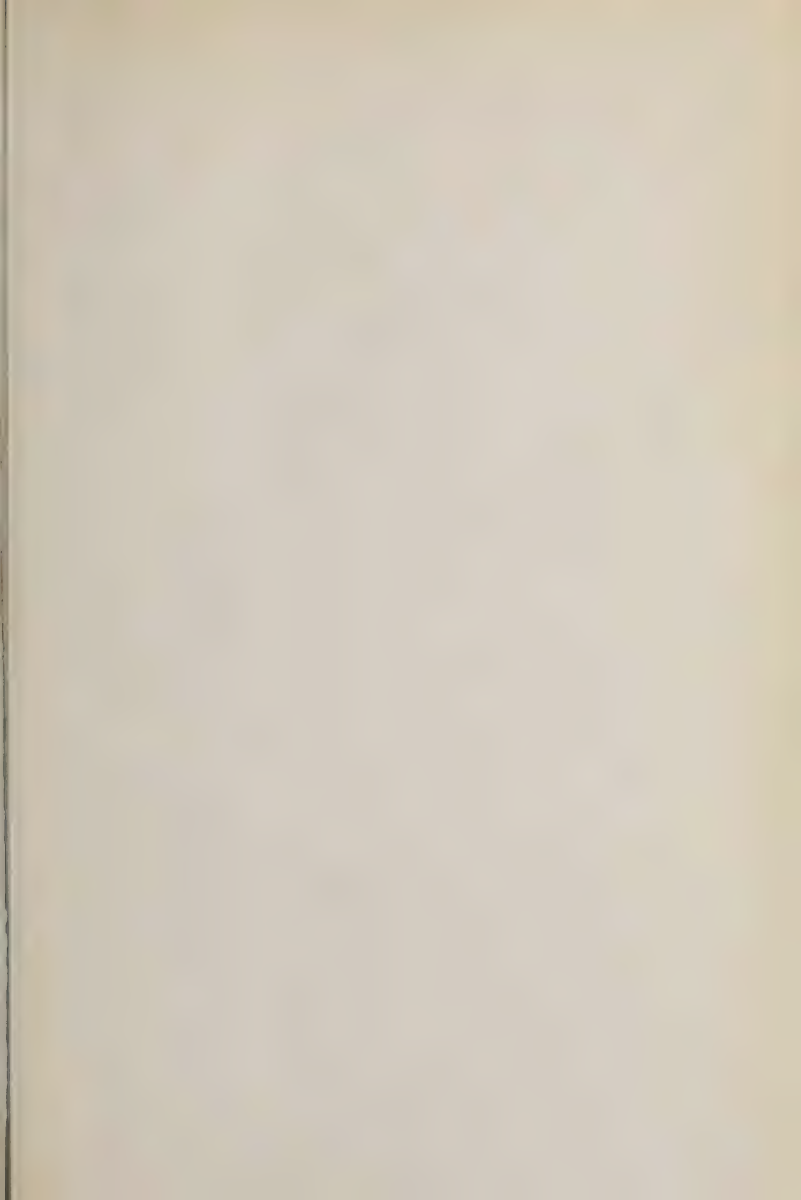
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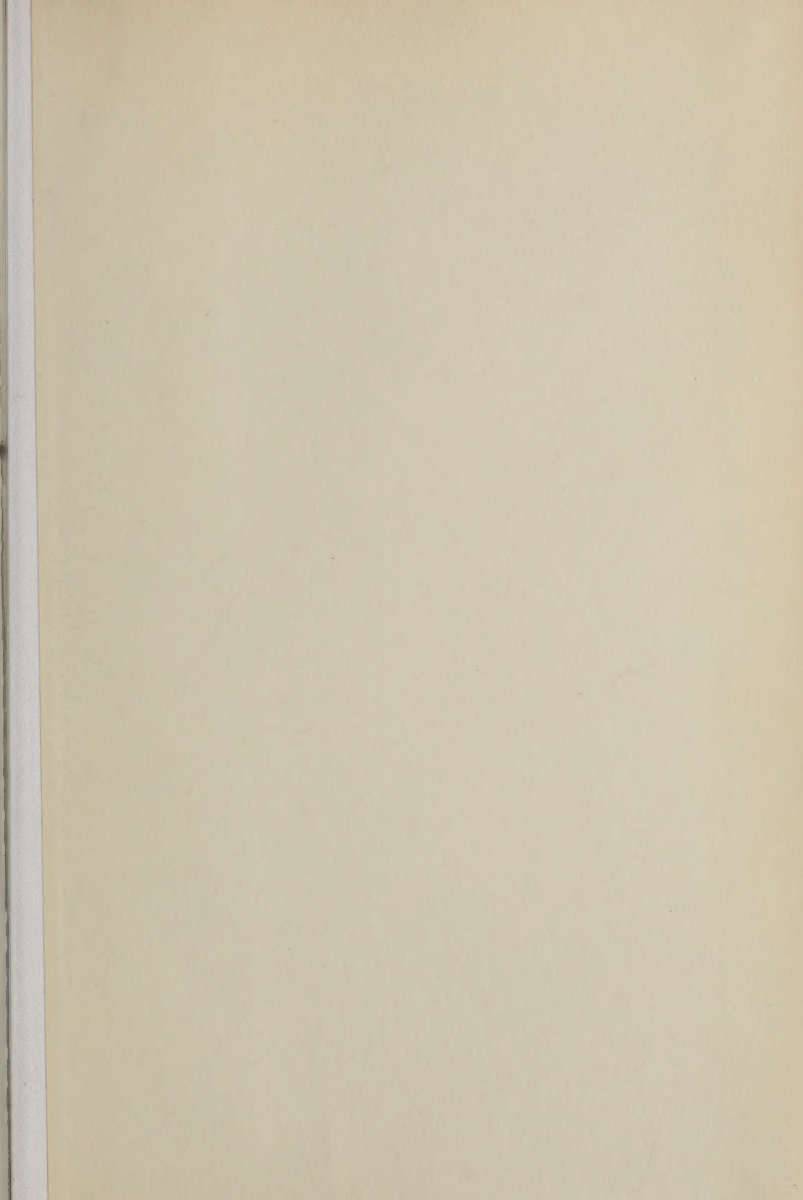
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